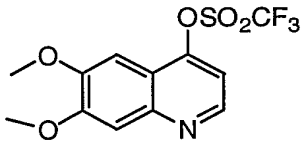
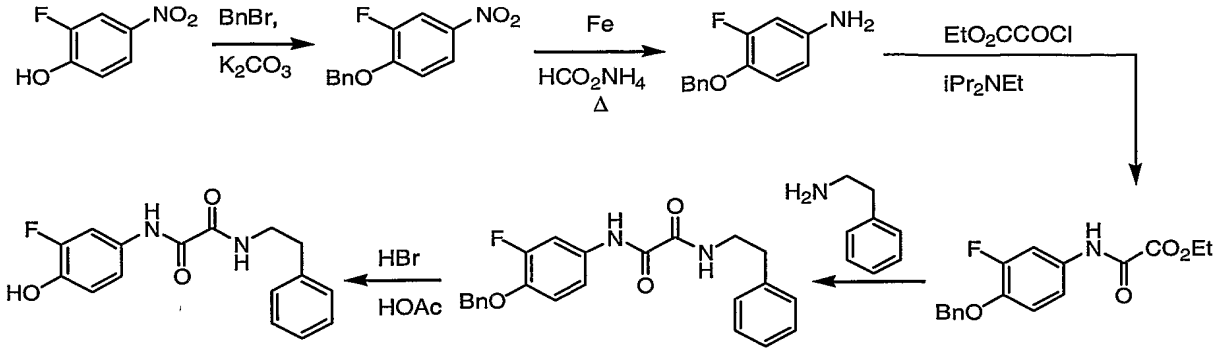
534 mmol). The mixture was cooled to –20°C by controlled addition of dry ice to an acetone bath. Trifluoromethanesulfonyl chloride (37 mL, 350 mmol) was added dropwise to the cooled solution with magnetic stirring over 25 minutes. After addition was complete, the mixture was stirred in bath for 20 minutes, then at room temperature for 3 hours. LCMS indicated reaction completion. The reaction mixture was concentrated *in vacuo* and placed under high vacuum to remove residual 2,6-lutidine. To the resulting brown solids was added methanol (3.5 L). The resulting slurry was stirred with mechanical stirrer for 30 min before adding water (1.5 L). The solids were isolated by filtration, followed by a water wash. The resulting solid was dried under high vacuum overnight yielding trifluoromethanesulfonic acid 7-benzyloxy-6-methoxy-quinolin-4-yl ester as a light brown solid (92.2 g, 83.8%). ^{1}H NMR (400MHz, DMSO, d_6): δ 8.82 (d, 1H), 7.67 (s, 1H), 7.59 (d, 1H), 7.54-7.52 (m, 2H), 7.46-7.42 (m, 2H), 7.39-7.36 (m, 1H), 7.23 (s, 1H), 5.35 (s, 2H), 3.97 (s, 3H). LC/MS: M+H = 414.

Example 34



[0331] Trifluoromethanesulfonic acid 6,7-dimethoxyquinolin-4-yl ester from 6,7-Dimethoxy-quinolin-4-ol. To a dry 1L RBF containing 6,7-dimethoxy-quinolin-4-ol (20.9 g, 102 mmol), which can be prepared according to the procedure of Riegel, B. *(J. Amer. Chem. Soc.* 1946, *68*, 1264), was added DCM (500 mL), 4-dimethylaminopyridine (1.24 g, 10 mmol) and 2,6-lutidine (24 mL, 204 mmol). The mixture was vigorously stirred at RT. Trifluoromethanesulfonyl chloride (14 mL, 132 mmol) was added dropwise to the solution. After addition was complete, the mixture was stirred ice bath for 2 to 3 hrs. On LC/MS indicating the reaction completion, the reaction mixture was concentrated *in vacuo* and placed under high vacuum to remove residual 2,6-lutidine. To the resulting brown solids was added methanol (250 mL). The resulting slurry was stirred for 30 min before adding water (1 L). The solids were isolated by filtration, followed by a water wash. The resulting solid was dried under high vacuum overnight yielding trifluoromethanesulfonic acid 6, 7-dimethoxy-quinolin-4-yl ester as a light brown solid (27 g, 80%). ^{1}H NMR (400MHz, DMSO, d_6): δ 8.82 (d, 1H), 7.59 (m, 2H), 7.20 (s, 1H), 3.97 (d, 6H). LC/MS: M+H = 338.

Example 35



[0332] 1-Benzyloxy-2-fluoro-4-nitrobenzene. A solution of 2-fluoro-4-nitrophenol (50.0 g, 318 mmol), benzyl bromide (42 mL, 350 mmol) and potassium carbonate (66.0 g, 478 mmol) in DMF (200 mL) was heated to 40 °C overnight. The solution was cooled to room temperature, poured over ice and the resultant solid was filtered. This material was washed with water and dried to give 1-benzyloxy-2-fluoro-4-nitrobenzene (75.0 g, 95 %). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.19-8.11 (m, 2H), 7.53-7.37 (m, 6H), 5.36 (s, 2H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 152.8, 152.4, 149.9, 140.9, 136.1, 129.3, 129.1, 128.7, 122.0, 115.2, 112.8, 112.6, 71.6; IR (cm^{-1}): 1499, 1346, 1279, 1211, 1142, 1072, 986, 885, 812, 789, 754, 742, 700, 648, 577.

[0333] 4-Benzyloxy-3-fluoroaniline. A mixture of iron powder (45.2 g, 0.809 g atoms), ammonium formate (53.6 g, 0.850 mol), 1-benzyloxy-2-fluoro-4-nitrobenzene (50.0 g, 0.200 mol), toluene (400 mL) and water (400 mL) was heated to reflux overnight. The mixture was filtered through Celite and washed with hot ethyl acetate. The combined organic layers were washed with water and brine, then dried over sodium sulfate and concentrated to afford 4-benzyloxy-3-fluoroaniline (44 g, 100 %). ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.43-7.26 (m, 5H), 6.90 (dd, 1H), 6.49 (dd, 1H), 6.34 (m, 1H), 4.99 (br s, 2H), 4.98 (s, 2H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 171.1, 155.1, 152.7, 144.9, 138.0, 137.2, 129.6, 129.0, 128.5, 118.9, 110.0, 102.9, 72.5; IR (cm^{-1}): 1510, 1454, 1277, 1215, 1126, 1007, 957, 843, 800, 789, 739, 694, 604; LC/MS (M+H = 218).

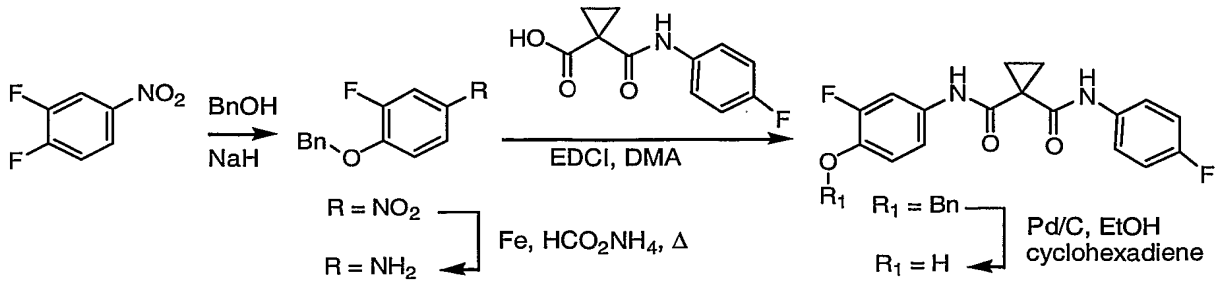
[0334] Ethyl [(4-benzyloxy-3-fluorophenyl)amino](oxo)acetate. Ethyl oxalyl chloride (44 mL, 390 mmol) was added to a solution of 4-benzyloxy-3-fluoroaniline (44 g, 180 mmol) in diisopropylethylamine (69 mL, 400 mmol) and stirred at room temperature for 15 min. The mixture was extracted with dichloromethane and washed with water and brine. The organic layer was dried over sodium sulfate and concentrated to afford ethyl [(4-

benzyloxy-3-fluorophenyl)amino](oxo)acetate (58.4 g, 100 %). ^{1}H NMR (400 MHz, d_6-DMSO): δ 10.87 (s, 1H), 7.73 (d, 1H), 7.69 (d, 1H), 7.53 (d, 1H), 7.46-7.40 (m, 4H), 5.17 (s, 2H), 4.31 (q, 2H), 1.31(t, 3H); IR (cm^{-1}): 1732, 1705, 1558, 1541, 1508, 1456, 1273, 1186, 1167, 1101, 999, 858, 741, 694; LC/MS (M+H = 318).

[0335] *N*-(4-Benzyloxy-3-flourophenyl)-*N'*-(2-phenylethyl)ethanediamide. Phenethylamine (33 mL, 520 mmol) was added to ethyl [(4-benzyloxy-3-fluorophenyl)amino](oxo)acetate (81 g, 260 mmol) and the mixture was sonicated at room temperature for 30 min. The resulting solid was filtered, washed with water and dried to give *N*-(4-benzyloxy-3-flourophenyl)-*N'*-(2-phenylethyl)ethanediamide (100 g, 99 %). ^{1}H NMR (400 MHz, d_6-DMSO): δ 10.72 (br s, 1H), 9.05 (m, 1H), 8.78 (m, 1H), 7.77 (m, 1H), 7.59 (m, 1H), 7.46-7.19 (m, 8H), 5.16 (m, 2H), 3.45 (m, 2H), 2.83 (m, 2H); IR (cm^{-1}): 2980, 2883, 1653, 1522, 1506, 1441, 1385, 1221, 1122, 951, 808, 746, 696, 584; LC/MS (M+H = 393).

[0336] *N*-(3-Fluoro-4-hydroxyphenyl)-*N'*-(2-phenylethyl)ethanediamide. A mixture of *N*-(4-benzyloxy-3-flourophenyl)-*N'*-(2-phenylethyl)ethanediamide (40 g, 100 mmol) and 38% hydrobromic acid in acetic acid (250 mL) was stirred at room temperature overnight. The resulting solid was filtered, washed with water and dried to give *N*-(3-fluoro-4-hydroxyphenyl)-*N'*-(2-phenylethyl)ethanediamide as a slightly yellow solid (30.6 g, 99 %yield). ^{1}H NMR (400 MHz, d_6-DMSO): δ 10.60 (s, 1H), 9.02 (t, 1H), 7.70 (d, 1H), 7.47 (d, 1H), 7.32-7.20 (m, 3H), 6.91 (t, 1H), 3.43 (m, 2H), 2.81 (m, 2H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 160.5, 158.8, 152.0, 149.6, 142.2, 139.8, 130.3, 129.3, 129.0, 126.8, 118.1, 117.4, 109.6, 109.3 IR (cm^{-1}): 3279, 1653, 1518, 1456, 1279, 1190, 742, 696, 584; LC/MS (M+H = 303).

Example 36



[0337] 1-Benzyloxy-2-fluoro-4-nitro-benzene. To a slurry of sodium hydride (60% dispersion is oil, 693 mmol, 27.7 g) and dimethylacetamide (600 ml) was added benzyl alcohol (462 mmol, 48 ml) dropwise with stirring under N_2. The mixture was stirred for 1 hour at RT and then cooled to 0°C. 3,4-difluoronitrobenzene (508 mmol, 56.2 ml) was added to the cooled solution and stirred for 1 hour. Reaction mixture poured onto saturated ammonium chloride solution (800 ml) and stirred for 30 minutes, filtered and washed with water. The solid was stirred in ethyl acetate (500 mL), and filtered to give 54g of product. The ethyl acetate filtrate, after concentrated in vacuo, was triturated with diethyl ether (500 mL), sonicated for 2 hours, and filtered to give another 30g of product. The ether layer was concentrated and column purified using 5% EtOAc/hexanes as eluent to gave additional 15g of product. The total yield of 1-benzyloxy-2-fluoro-4-nitro-benzene was 95g (83%). (Note: the product contains ca. 5% of 3,4-Bis-benzyloxy-nitrobenzene, which is carried into the next step without further purification.) ^{1}H NMR (400MHz, $CDCl_3$): δ 8.04 –8.00 (m, 2H), 7.43-7.37 (m, 5H), 7.08 (t, 1H), 5.26 (s, 2H).

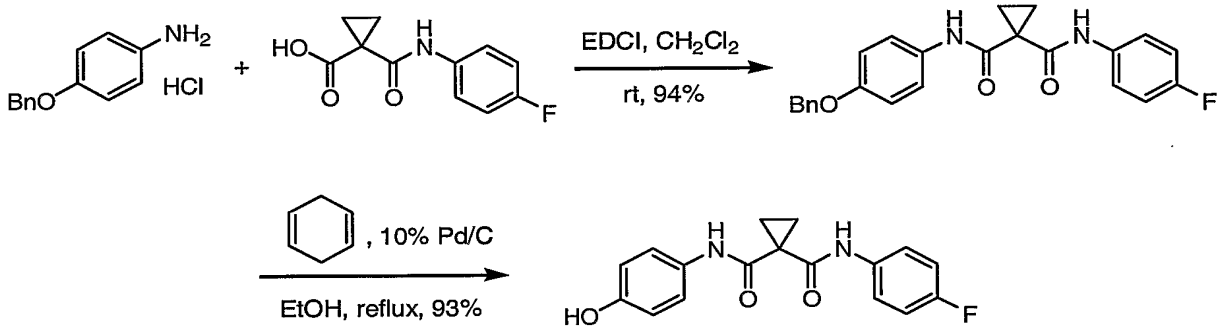
[0338] 4-Benzyloxy-3-fluoro-phenylamine. A mixture of 1-benzyloxy-2-fluoro-4-nitro-benzene (44g, 178 mmol), toluene (400 ml), ammonium formate (35 g), iron (30 g), and water (400 ml) was heated to reflux with stirring overnight. The reaction mixture was filtered through celite and washed with ethyl acetate (400ml). The organic layer was separated and washed with brine (300 ml), dried over sodium sulfate and concentrated to give 4-benzyloxy-3-fluoro-phenylamine as an oil (33.7 g, 87%). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.41-7.29 (m, 5H), 6.79 (t, 1H), 6.45 (dd, 1H), 6.14 (dd, 1H), 5.02 (s, 2H), 3.50 (s, 2H). LC/MS: (M+1) 218.

[0339] Cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-3-fluoro-phenyl)-amide (4-fluoro-phenyl)-amide. To a stirred mixture of 4-benzyloxy-3-fluoro-phenylamine (155.3 mmol, 33.7 g), 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (170.8 mmol, 38.13 g) and anhydrous dichloromethane (600 ml) was added EDCI (233.9 mmol, 44.7 g) in portions. After stirring at RT for 1 hr, the reaction mixture was diluted with saturated sodium bicarbonate (400 ml) and stirred for 30 minutes. The precipitate was filtered and air dried to give the 1st crop of product. The biphasic filtrate was separated, and the organic phase was washed with brine (300 ml), dried over sodium sulfate, and concentrated. The residue was taken up in DCM (100 ml), stirred for 15 minutes, and filtered to give a 2nd crop of product. The combined yield of cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-3-fluoro-phenyl)-amide (4-fluoro-phenyl)-amide was 64.5

g (98%). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.92 (br s, 1H), 8.88 (br s, 1H), 7.50-7.32 (m, 8H), 7.06-7.02 (m, 3H), 6.97-6.92 (t, 1H), 5.13 (s, 2H), 1.65 (s, 4H). LC/MS: (M+1) 423.

[0340] Cyclopropane-1,1-dicarboxylic acid (3-fluoro-4-hydroxy-phenyl)-amide (4-fluoro-phenyl)-amide. A mixture of cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-3-fluoro-phenyl)-amide (4-fluoro-phenyl)-amide (152.8 mmol, 64.5), ethanol (800 ml), cyclohexadiene (764 mmol, 71 ml), and 10% Pd/C (2 g) was refluxed for 2 hours. Reaction mixture cooled and filtered through celite and washed with methanol. The combined filtrate was concentrated and stirred in 10% EtOAc/ether (350 ml). The resulting precipitate was filtered and washed with ether to give a 1st crop of product. The filtrate was concentrated and stirred in DCM (150 ml) to give another precipitate, which was then filtered to give a 2nd crop of product. The combined yield of cyclopropane-1,1-dicarboxylic acid (3-fluoro-4-hydroxy-phenyl)-amide (4-fluoro-phenyl)-amide was 43 g (85%) in 95% purity by HPLC (UV @ 254 nm). ^{1}H NMR (400MHz, DMSO-D6): δ 10.07 (br s, 1H), 9.92 (br s, 1H), 9.64 (br s, 1H), 7.64-7.60 (m, 2H), 7.55-7.51 (m, 1H), 7.17-7.12 (m, 3H), 6.89-6.84 (t, 1H), 1.43 (s, 4H). LC/MS: (M+1) 333.

Example 37

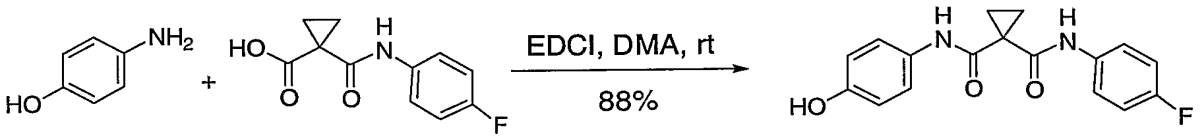


[0341] Cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-phenyl)-amide (4-fluoro-phenyl)-amide. To a 0 °C suspension of 4-benzyloxyaniline hydrochloride (47.0 g, 200 mmol) and 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (49.1 g, 220 mmol) in CH_2Cl_2 (400 mL) was added EDCI (38.2 g, 200 mmol). Stirring was continued at rt for 2-4 h until the reaction was complete. CH_2Cl_2 was removed under reduced pressure. H_2O (300 mL) and MeOH (200 mL) were added, and the resulting mixture was stirred at rt for 30 min. After filtration and wash with H_2O, the solid was transferred to another flask containing 300 mL of sat. aqueous $NaHCO_3$ solution. The mixture was stirred for another 30 min. The solid was filtered, washed with water, and dried over night

on a lyophilizer, affording cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-phenyl)-amide (4-fluoro-phenyl)-amide (75.8g, 95% yield) as an off-white solid.

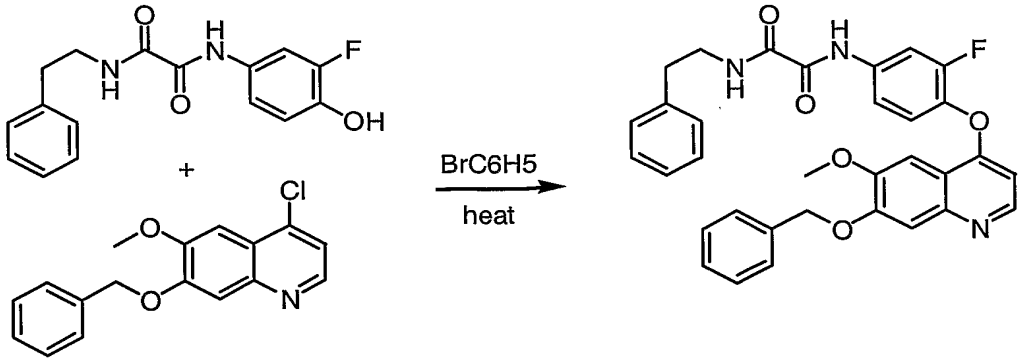
[0342] Cyclopropane-1,1-dicarboxylic acid (4-fluoro-phenyl)-amide (4-hydroxy-phenyl)-amide. To a refluxing mixture of cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-phenyl)-amide (4-fluoro-phenyl)-amide (46 g, 113 mmol), 10% Pd/C (2 g) in EtOH (400 mL) was added dropwise 1,4-cyclohexadiene (62.7 mL, 678 mmol). Stirring was continued for 2-5 h until the reaction was complete. The mixture was cooled to rt, filtered through celite, and washed with EtOH. The solution was then concentrated under reduced pressure. To the flask containing the crude product was added $CHCl_3$ (200 mL). The resulting suspension was stirred for 15 min at rt. The solid was filtered, and dried in the air to give cyclopropane-1,1-dicarboxylic acid (4-fluoro-phenyl)-amide (4-hydroxy-phenyl)-amide (34.4 g, 95%, yield).

Example 38



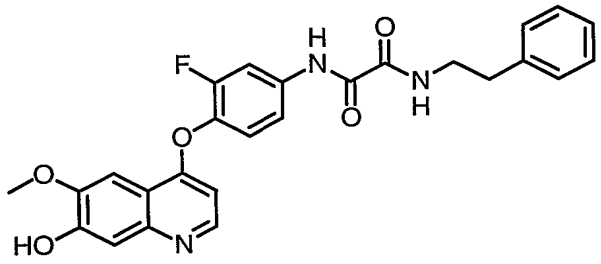
[0343] Alternate Synthesis of Cyclopropane-1,1-dicarboxylic acid (4-fluoro-phenyl)-amide (4-hydroxy-phenyl)-amide. To a solution of 4-aminophenol (2.93 g, 26.9 mmol) and 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (5.00 g, 22.4 mmol) in DMA (30 mL) was added EDCI (5.15 g, 26.9 mmol). The mixture was stirred vigorously until the reaction was complete (~ 3 h). With vigorous stirring, the reaction mixture was then poured into a flask containing sat. aqueous $NaHCO_3$ solution (200 mL). The stirring was continued for 1 h. The resulting suspension was then filtered. The solid was washed with water (50 mL), chloroform (50 mL) and dried under vacuum, affording 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (6.22g, 88% yield) as a powder (>95% purity by HPLC and ^1H NMR).

Example 39



[0344] *N*-{4-[(7-Benzyloxy-6-methoxyquinolin-4-yl)oxyl-3-fluorophenyl}-*N'*-(2-phenylethyl)ethanediamide. A mixture of 7-benzyloxy-4-chloro-6-methoxyquinoline (30 g, 100 mmol), *N*-(3-fluoro-4-hydroxyphenyl)-*N'*-(2-phenylethyl)ethanediamide (32 g, 106 mmol), DMAP (125 g, 1.02 mol) and bromobenzene (500 mL) was heated to reflux for 6 h. The mixture was cooled to room temperature and the bromobenzene was removed under reduced pressure. Methanol (500 mL) was added to the residue and the mixture was stirred at room temperature for 2 h. The resulting solid was filtered, washed with methanol and dried to give *N*-{4-[(7-benzyloxy-6-methoxyquinolin-4-yl)oxy]-3-fluorophenyl}-*N'*-(2-phenylethyl) ethanediamide (34 g, 61 %). ^{1}H NMR (400 MHz, d_6-DMSO): δ 11.05 (s, 1H), 9.15 (s, 1H), 8.47 (d, 1H), 8.05 (d, 1H), 7.84 (d, 1H), 7.56-6.36 (m, 13H), 6.46 (d, 1H), 5.32 (s, 2H), 3.97 (s, 3H), 3.47 (q, 2H), 2.86 (t, 2H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 160.5, 160.2, 159.9, 159.5, 155.2, 152.7, 152.2, 150.3, 149.6, 146.9, 139.7, 137.4, 137.3, 137.2, 137.1, 129.3, 129.2, 129.1, 129.0, 128.9, 128.7, 128.6, 126.9, 124.8, 117.9, 115.3, 109.9, 102.8, 99.8, 70.6, 56.5, 41.3, 35.2; IR (cm^{-1}): 1657, 1510, 1481, 1433, 1416, 1352, 1310, 1252, 1215, 1609, 986, 891, 868, 850, 742, 696; LC/MS (M+H = 566).

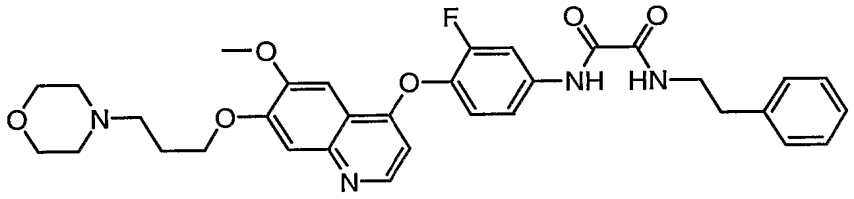
Example 40



[0345] *N*-{3-Fluoro-4-[(7-hydroxy-6-methoxyquinolin-4-yl)oxy]phenyl}-*N'*-(2-phenylethyl)ethanediamide. To a solution of *N*-{4-[(7-benzyloxy-6-methoxyquinolin-4-

yl)oxy]-3-fluorophenyl}-*N'*-(2-phenylethyl)ethanediamide (32 g, 56 mmol) in methanol (200 mL), DMF (100 mL), dichloromethane (100 mL), ethyl acetate (100 mL) and acetic acid (5 mL) was added palladium hydroxide (4.2 g) and the mixture was shaken on a Parr hydrogenator under a hydrogen pressure of 45 psi for 4 h. The resulting suspension was filtered through celite and the solid residue was washed with boiling dichloromethane (2 L) and acetone (2 L). The combined filtrates were evaporated to yield *N*-{3-fluoro-4-[(7-hydroxy-6-methoxyquinolin-4-yl)oxy]phenyl}-*N'*-(2-phenylethyl)ethanediamide as an off-white solid (25.6 g, 95 %). ^{1}H NMR (400 MHz, d_6-DMSO): δ 11.06 (s, 1H), 10.25 (br s, 1H), 9.12 (t, 1H), 8.40 (d, 1H), 8.01 (dd, 1H), 7.50-7.44 (m, 2H), 7.31-7.23 (m, 6H), 6.39 (d, 1H), 3.95 (s, 3H), 2.85 (t, 2H), 2.50 (m, 2H); IR (cm-1): 1666, 1624, 1585, 1520, 1481, 1427, 1377, 1256, 1211, 1194, 1022, 880, 850, 839, 802, 750, 700; LC/MS (M+H = 476).

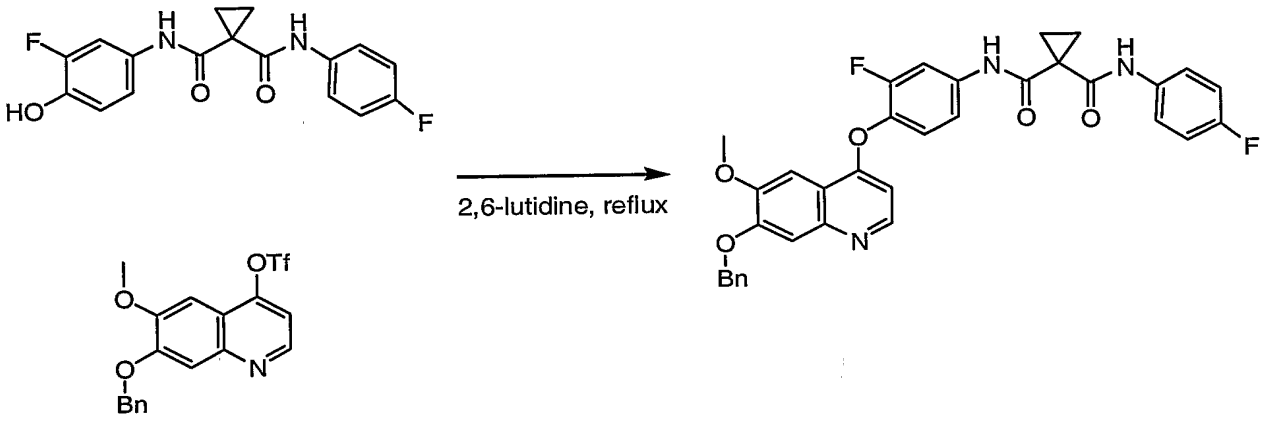
Example 41



[0346] *N*-(3-Fluoro-4-{[6-methoxy-7-(3-morpholin-4-ylpropoxy)quinolin-4-yl]oxy}phenyl)-*N'*-(2-phenylethyl)ethanediamide. A solution of *N*-{3-fluoro-4-[(7-hydroxy-6-methoxyquinolin-4-yl)oxy]phenyl}-*N'*-(2-phenylethyl)ethanediamide (25.6 g, 54 mmol), *N*-(3-chloropropyl)morpholine hydrochloride (11.7 g, 592 mmol) and potassium carbonate (16.6 g, 120 mmol) in DMF (300 mL) was heated to 80 °C overnight. Upon cooling, a majority of the DMF (250 mL) was removed on a rotary evaporator, 5% aqueous LiCl (300 mL) was added and the mixture was sonicated at room temperature. The solid was filtered, suspended in 1N HCl and washed with ethyl acetate (2 x 300 mL). The solution was adjusted to pH 14 using 2N sodium hydroxide and subsequently extracted with dichloromethane (3 x 200 mL). The organic layer was dried over sodium sulfate, filtered and evaporated to give *N*-(3-fluoro-4-{[6-methoxy-7-(3-morpholin-4-ylpropoxy)quinolin-4-yl]oxy}phenyl)-*N'*-(2-phenylethyl)ethanediamide as a yellow solid (24 g, 74 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.37 (s, 1H), 8.46 (d, 1H), 7.81 (dd, 1H), 7.57 (t, 1H), 7.53 (s, 1H), 7.42 (s, 2H), 7.34-7.20 (m, 6H), 6.39 (d, 1H), 4.27 (t, 2H), 4.03 (s, 3H), 3.71 (m, 4H), 3.65 (q, 2H), 2.91 (t, 2H), 2.56 (br s, 4H), 2.13 (m, 2H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 160.1, 160.0, 159.5, 155.2, 152.7, 152.6, 150.2, 149.5, 147.1,

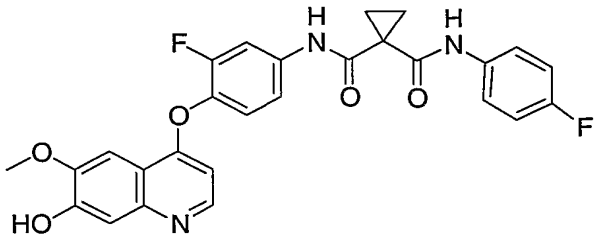
139.7, 137.3, 137.1, 129.3, 129.1, 126.9, 124.8, 117.9, 115.1, 109.2, 102.7, 99.6, 67.4, 66.9, 56.5, 55.5, 54.1, 41.3, 35.2, 26.4; IR (cm^{-1}): 1655, 1506, 1483, 1431, 1350, 1302, 1248, 1221, 1176, 1119, 864, 843, 804, 741, 700; LC/MS (M+H = 603).

Example 42



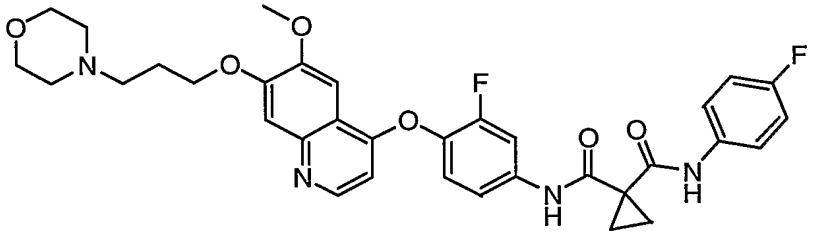
[0347] Cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide. To a flask containing cyclopropane-1,1-dicarboxylic acid (3-fluoro-4-hydroxy-phenyl)-amide (4-fluoro-phenyl)-amide (2.25 g, 6.7 mmol) and trifluoromethanesulfonic acid 7-benzyloxy-6-methoxy-quinolin-4-yl ester (1.87 g, 4.5 mmol) was added dry 2,6-lutidine (9 mL). The reaction mixture was heated to reflux (143°C) with vigorous stirring. The reaction progress was monitored by LC-MS. 2,6-Lutidine was removed under reduced pressure when the reaction was complete (about 6 h). The residue was treated with charcoal (1.5 g) in refluxing EtOAc (50 mL) for 15 min, and filtered through celite. The volume of the filtrate was reduced to about 20 mL and was added 20 mL of 1 N HCl. The crude product precipitated as the HCl salt, which was filtered and washed with EtOAc and H_2O (88% purity by analytical HPLC). The HCl salt was free-based with saturated aqueous $NaHCO_3$ solution. Further purification by column chromatography (hexans:EtOAc = 1:4) gave cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide as an off-white solid (1.3 g, 48% yield. ^1H NMR (400 MHz, DMSO, d_6): 10.41 (s, 1H), 10.02 (s, 1H), 8.48 (d, 1H), 7.92 (dd, 1H), 7.65 (m, 2H), 7.54 (m, 5H), 7.41 (m, 4H), 7.17 (m, 2H), 6.43 (d, 1H), 5.32 (s, 2H), 3.97 (s, 3H), 1.48 (m, 4H). LC/MS Calcd for $[M+H]^+$ 596.2, found 596.3.

Example 43



[0348] Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide. To a solution of the cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide (22.4 g, 37.6 mmol) in EtOH (340 mL) was added 1,4-cyclohexadiene (35 mL, 376 mmol) and 10% Pd/C (2.08 g). The reaction mixture was then heated at 65°C with stirring for 3 h (Caution: H_2 gas is released from the reaction). It was then allowed to cool to room temperature, and filtered through celite follwed by a MeOH wash. The solution was then concentrated under reduced pressure. The yellow residue was taken into EtOAc (1 L). The EtOAc solution was washed with water (1X), brine (2X), dried over $MgSO_4$ and concentrated *in vacuo*. Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide was obtained as a yellow solid (17.3 g, 91.1% yield), which were carried on to the next reaction without further purification. ^{1}H NMR (400 MHz, DMSO, d6): 10.39 (s, 1H), 10.15 (s, 1H), 10.00 (s, 1H), 8.38 (d, 1H), 7.88 (dd, 1H), 7.63 (m, 2H), 7.50 (m, 2H), 7.40 (t, 1H), 7.27 (s, 1H), 7.14 (m, 2H), 6.33 (d, 1H), 3.95 (s, 3H), 1.47 (m, 4H). LC/MS Calcd for $[M+H]^+$ 506.2, found 506.3. Anal. HPLC: 99.4% pure.

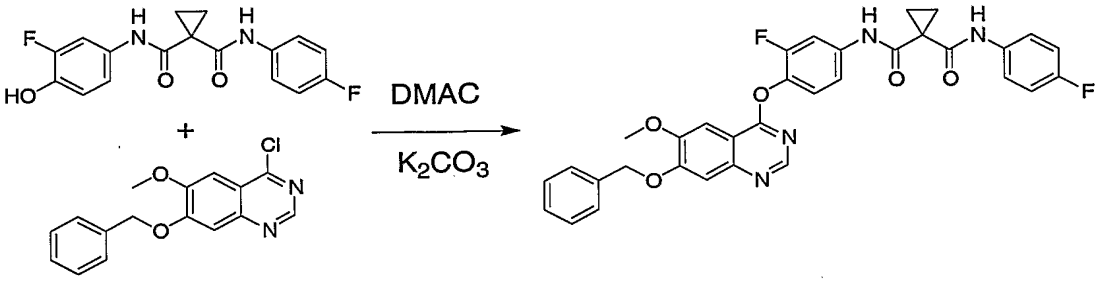
Example 44



[0349] *N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a mechanically stirred slurry of cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (16.6 g, 32.8 mmol) and

potassium carbonate (13.6 g, 98.6 mmol) in DMF (250 mL) was added 4-(3-chloropropyl)-morpholine hydrochloride (13, 7.92 g, 39.6 mmol). The resulting mixture was heated at 90°C for 5 hours (until phenol completely consumed). The reaction mixture was allowed to cool to room temperature, then dumped into water (900 mL), followed by extraction with EtOAc (3X). The combined extracts were washed with 5% LiCl (aq.) (3X) and brine (1X) followed by drying over MgSO4 and concentration in vacuo. The crude (18.8g) obtained as brown solid was further purified by flash chromatography [silica gel, 4-stage gradient system: 1) EtOAc; 2) EtOAc:MeOH:7N NH_3/MeOH (95:5:0.5); 3) DCM:MeOH:7N NH3/MeOH (95:5:0.5); 4) DCM:MeOH: 7N NH_3/MeOH (93:8:1)], affording N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide was obtained as an off white solid (15.0 g, 72% yield). 1H NMR (400 MHz, DMSO-d6): 10.41 (s, 1H), 10.02 (s, 1H), 8.47 (d, 1H), 7.91 (dd, 1H), 7.65 (m, 2H), 7.53 (m, 2H), 7.42 (t, 1H), 7.40 (s, 1H), 7.16 (m, 2H), 6.42 (d, 1H), 4.20 (t, 2H), 3.96 (s, 3H), 3.59 (t, 4H), 2.47 (t, 2H), 2.39 (br, s, 4H), 1.98 (m, 2H), 1.48 (m, 4H). LC/MS Calcd for [M+H]+ 633.3, found 633.0.

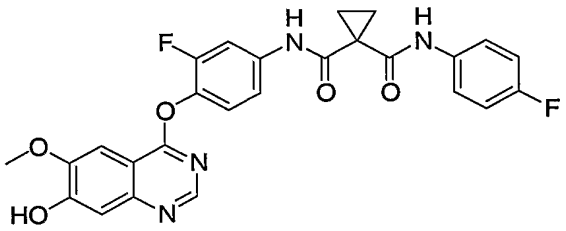
Example 45



[0350] Cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinazolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide: A mixture of 7-benzyloxy-4-chloro-6-methoxy-quinazoline (5 g, 16.67 mmol), cyclopropane-1,1-dicarboxylic acid (3-fluoro-4-hydroxy-phenyl)-amide (4-fluoro-phenyl)-amide (8.3 g, 25 mmol), potassium carbonate (125 mmol, 17.25 g), and dimethylacetamide (125 ml) was heated 50° C with stirring for 16h. Reaction mixture was poured onto ice/water (600 ml) and stirred for 30 minutes, and filtered. The solid was dissolved in ethyl acetate and washed with water (1x), brine, and concentrated. The crude was purified on silica get column eluting with 30% acetone in hexanes to yield cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-

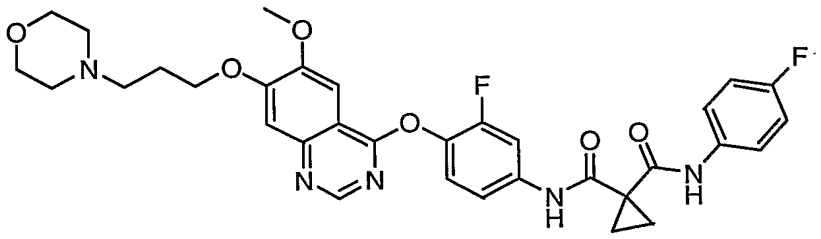
methoxy-quinazolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide (7.5 g, 76%). ^{1}H NMR ($CDCl_3$): 8.64 (1H, br. s), 8.55 (1H, s), 8.33 (1H, br. s), 7.74-7.71 (1H, dd), 7.54 (1H, s), 7.48-7.33 (8H, m), 7.31-7.24 (2H, m), 7.06-7.02 (2H, m), 5.32 (2H, s), 4.06 (3H, s), 1.77-1.74 (2H, m), 1.63-1.61 (2H, m).

Example 46



[0351] Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide. To a mixture of cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinazolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide (7.5 g, 12.6 mmol), acetic acid (few drops), dichloromethane (50 ml) and methanol (100 ml) was added 10% Pd/C (700 mg). The mixture was agitated in hydrogen gas (40 psi) until the reaction was complete (ca. 4 hr). The solution was filtered through celite and concentrated to give a crude product as a solid. The crude product was triturated with ether, and filtered. The filter cake was dried *in vacuo* to yield cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (6.1 g, 95% yield). ^{1}H NMR (dmso-d6): 10.86 (1H, br. s), 10.34 (1H, br. s), 10.04 (1H, br. s), 8.46 (1H, s), 7.84-7.80 (1H, dd), 7.66-7.62 (2H, m), 7.55 (1H, s), 7.47-7.45 (1H, m), 7.41-7.37 (1H, m), 7.24 (1H, s), 7.18-7.13 (2H, t), 3.98 (3H, s), 1.46 (4H, s).

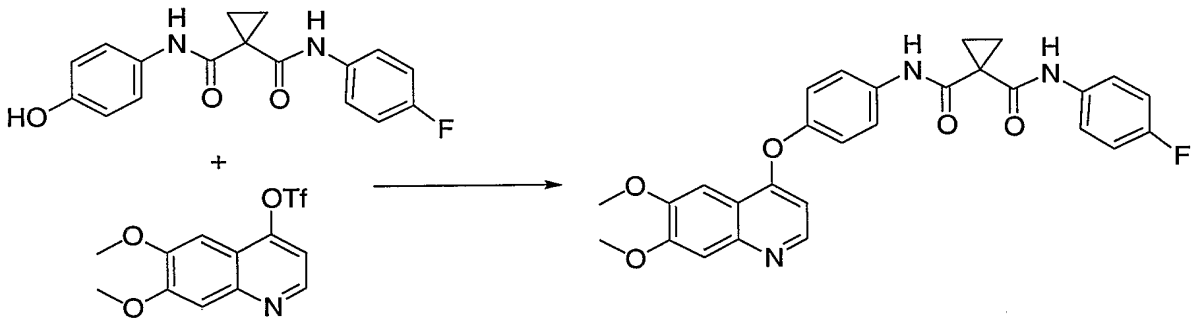
Example 47



[0352] N-[3-Fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a mixture of

cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (1.5 g, 2.96 mmol), 4-(3-hydroxypropyl)morpholine (0.623 mL, 4.5 mmol), triphenylphosphine (1.18 g, 4.5 mmol), and dichloromethane (50 mL) was added diisopropyl azodicarboxylate (0.886 mL, 4.5 mmol). The mixture was stirred at room temperature for 16 h, monitored by LCMS. After removal of solvent, the crude mixture was separated by flash column chromatography (silica), eluting with 5% methanol in dichloromethane to give N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarbox-amide (890 mg, 47% yield). 1HNMR (400MHz, DMSO-d6): d 10.36 (br s, 1H), 10.05 (br s, 1H), 8.55 (s, 1H), 7.83 (m, 1H), 7.64 (m, 2H), 7.57 (s, 1H), 7.44 (m, 3H), 7.18 (t, 2H), 4.27 (m, 2H), 3.99 (s, 3H), 3.61 (m, 6H), 2.40 (m, 4H), 2.01 (m, 2H), 1.47 (m, 4H). LC/MS Calcd for $[M+H]^+$ 634.2, found 634.3.

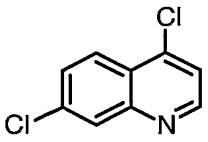
Example 48



[0353] N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a solution of cyclopropane-1,1-dicarboxylic acid (4-fluoro-phenyl)-amide (4-hydroxy-phenyl)-amide (6.98 g, 22.2 mmol) in anhydrous 2,6-lutidine (50 mL) was added trifluoromethanesulfonic acid 6, 7-dimethoxy-quinolin-4-yl ester (5 g, 14.8 mmol). The reaction mixture was heated at 165°C in a sealed pressure tube with stirring for 18 h. The reaction mixture was concentrated on high vacuum to completely remove lutidine. The resulting solid material was dissolved in DCM (250 mL), and washed several times with 1 N sodium hydroxide to remove the excess phenol. The crude mixture was loaded on a silica gel flash column and eluted with 75% EtOAc-hexanes, affording N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (3.2 g, 44%). ^{1}H NMR (400 MHz, d_6-DMSO): δ 10.2 (s, 1H), 10.05 (s, 1H), 8.4 (s, 1H), 7.8 (m, 2H), 7.65 (m, 2H), 7.5 (s, 1H),

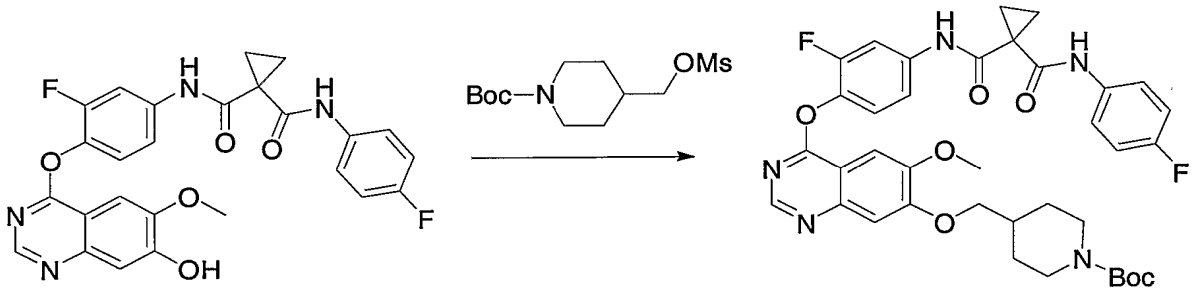
7.35 (s, 1H), 7.25 (m, 2H), 7.15(m, 2H), 6.4 (s, 1H), 4.0 (d, 6H), 1.5 (s, 4H). LC/MS: M+H= 502.

Example 49



[0354] 4,7-Dichloroquinoline. Phosphorus oxychloride (4mL, 429 mmol) was added to 7-chloro-4-hydroxyquinoline 2.86g, 15.9mmol) in a round bottom flask equipped with a reflux condenser. The mixture was heated to reflux for 2h, then allowed to cool to room temperature. The solution was concentrated *in vacuo* to a thick oil, then dumped over cracked ice. The resulting solution was neutralized with saturated $NaHCO_3$ (aq). The slurry was filtered and washed with water. The solids were dried under vacuum, afforded 4,7-dichloroquinoline as a white solid (2.79g, 88.5% yield).

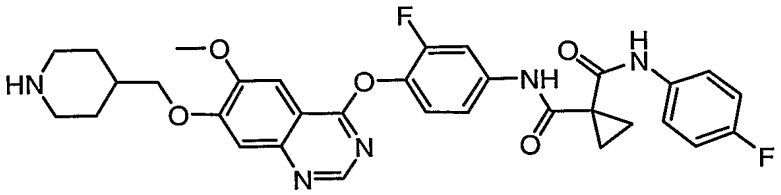
Example 50



[0355] 4-[4-(2-Fluoro-4-{[1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl]-amino}-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester. Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (325 mg, 0.64 mmol), 4-methanesulfonyloxymethyl-piperidine-1-carboxylic acid tert-butyl ester (193 mg, 0.66 mmol), K_2CO_3 (181 mg, 1.31 mmol) were combined in DMF (5 ml) and heated to 80°C overnight. The reaction was not complete and more 4-methanesulfonyloxymethyl-piperidine-1-carboxylic acid tert-butyl ester (90 mg, 0.31 mmol) and K_2CO_3 (90 mg, 0.65 mmol) were added and heating at 80°C continued for another night. The reaction mixture

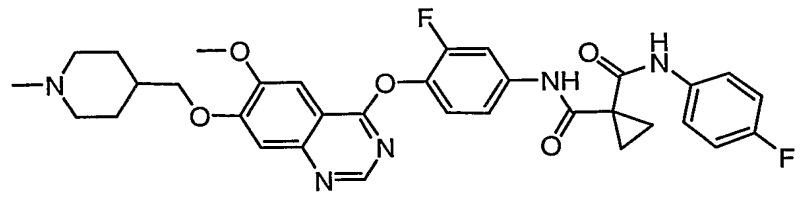
was allowed to cool to room temperature, then diluted with EtOAc and washed with H_2O (3x), sat'd NaCl (1x), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting crude material was purified by flash chromatography (1:1 hexanes:EtOAc, followed by 1:3 hexanes:EtOAc) to give 4-[4-(2-fluoro-4-{[1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl]-amino}-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester (273 mg, 60%). LC/MS Calcd for $[M+H]^+$ 704.3, found 704.4.

Example 51



[0356] Cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxyl-phenyl}-amide (4-fluoro-phenyl)-amide, TFA salt. 4-[4-(2-Fluoro-4-{[1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl]-amino}-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester (273 mg, 0.39 mmol) was dissolved in CH_2Cl_2 (8 ml) to which was added TFA (8 ml) and the mixture stirred at room temperature for 1hr. The reaction mixture was concentrated *in vacuo* and the resulting oil triturated with Et_2O. The resulting solids were filtered, washed with Et_2O and dried under high vacuum to give cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-amide (4-fluoro-phenyl)-amide, TFA salt (222 mg, 80%). LC/MS Calcd for $[M+H]^+$ 604.2, found 604.3.

Example 52



[0357] N-{3-Fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

Cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-amide (4-fluoro-phenyl)-amide, TFA salt (222 mg, 0.31 mmol), H_2O (3 ml), 37% formaldehyde in H_2O (0.18 ml) and acetic acid (27 drops) were combined in acetonitrile (9 ml) to which was slowly added triacetoxyborohydride (561 mg, 2.65 mmol). The mixture was stirred at room temperature for 1-2 hr, then diluted with 1N NaOH and H_2O and extracted with CH_2Cl_2 (3x). The combined CH_2Cl_2 extractions were washed with sat'd NaCl (1x), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was dissolved in a minimum of 1:1 dioxane:EtOAc to which was added 4M HCl in dioxane (1-2 ml). The resulting solids were filtered, washed with EtOAc and dried under high vacuum to give N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy] phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, HCl salt (167 mg, 83%). 1HNMR (400MHz, DMSO-d_6): δ 10.40 (s, 1H), 10.17 (br s, 1H) 10.07 (s, 1H), 8.61 (s, 1H), 7.85 (m, 1H), 7.65 (m, 2H), 7.48 (m, 2H), 7.42 (t, 1H), 7.16 (t, 2H), 4.12 (2, 2H), 4.00 (s, 3H), 3.46 (m, 2H), 2.99 (m, 2H), 2.73 (d, 3H), 2.13 (m, 1H), 2.01 (m, 2H), 1.63 (m, 2H), 1.47 (m, 4H). LC/MS Calcd for $[M+H]^+$ 618.2, found 618.3.

Synthesis of Bridged Bicyclics

[0358] The following describes synthesis of bridged bicyclics with appended leaving groups for use as, for example, alkylating agents. In the context of this invention, these alkylating agents are used, for example, to alkylate the quinazoline or quinolines on the 6- or 7-oxygens to make compounds of the invention. The invention is not limited to alkylation chemistry to append such bridged bicyclics, but rather the aforementioned description is meant only to be illustrative of an aspect of the invention.

Example 53

[0359] 1,4:3,6-dianhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-D-glucitol: To a solution of 1,4:3,6-dianhydro-2-*O*-methyl-D-glucitol (1.19g, 7.4 mmol) in dichloromethane was added pyridine (1mL, 12.36 mmol) followed by methanesulfonyl chloride (0.69mL, 8.92 mmol) and the mixture was allowed to stir at room temperature over 12 hours. The solvent was removed and the amorphous residue was partitioned with ethyl acetate and 0.1M aqueous hydrochloric acid. The aqueous phase was extracted once with additional

ethyl acetate and the combined organic layers were washed with saturated aqueous sodium chloride then dried over anhydrous magnesium sulfate. Filtration and concentration followed by drying *in vacuo* afforded 1,4:3,6-dianhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-D-glucitol (1.67g, 94% yield) as a colorless oil. GC/MS calculated for $C_8H_{14}SO_6$: 238 (M^+).

Example 54

[0360] 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose ethylene glycol acetal: A solution of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose (2.00g, 8.06 mmol), ethylene glycol (5.00g, 80.6 mmol), and *p*-toluenesulfonic acid (1.53g, 8.06 mmol) in benzene (100mL) was refluxed for 90 min using a Dean-Stark Trap apparatus. The reaction mixture was diluted with ethyl acetate (100mL), washed with saturated aqueous sodium bicarbonate (2 x 50mL) then brine (50mL), and dried over anhydrous sodium sulfate. Filtration, concentration and column chromatography on silica (1:1 hexane/ethyl acetate) provided 1.44g (61% yield) of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose ethylene glycol acetal as a colorless solid. ^{1}H NMR (400 MHz; $CDCl_3$): 8.08 (m, 2H), 7.58 (m, 1H), 7.54 (m, 2H), 5.38 (dd, 1H), 4.97 (t, 1H), 4.21-4.02 (m, 7H), 3.86 (d, 1H), 3.75 (d, 1H).

Example 55

[0361] 1,4:3,6-dianhydro-D-fructose ethylene glycol acetal: To a solution of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose ethylene glycol acetal (1.44g, 4.93 mmol) in methanol (40mL) was added 50% aqueous sodium hydroxide (0.38 g, 4.75 mmol) and the mixture was stirred at room temperature for 30 minutes. Neutralization with 1M HCl, followed by concentration and column chromatography on silica (1:2 hexane/ethyl acetate) provided 0.74g (80% yield) of 1,4:3,6-dianhydro-D-fructose ethylene glycol acetal as a colorless solid. ^{1}H NMR (400 MHz; $CDCl_3$): 4.60 (t, 1H), 4.32 (m, 1H), 4.14 (d, 1H), 4.05-3.98 (m, 5H), 3.82 (s, 2H), 3.62 (dd, 1H), 2.65 (d, 1H).

[0362] 1,4:3,6-dianhydro-5-*O*-(methylsulfonyl)-D-fructose ethylene glycol acetal: To a solution of 1,4:3,6-dianhydro-D-fructose ethylene glycol acetal (0.74g, 3.93 mmol) and triethylamine (1.20g, 11.86 mmol) in dichloromethane (40mL) was added

methanesulfonyl chloride (0.90g, 7.88 mmol) at 0°C under nitrogen. The solution was warmed to room temperature and stirred for 13 h. Dichloromethane (50mL) was added, and the organic layer was washed with saturated aqueous sodium bicarbonate (30mL), water (30mL), and brine (30mL) then dried over anhydrous sodium sulfate. Filtration and concentration provided 1.02g (97%) of 1,4:3,6-dianhydro-5-*O*-(methylsulfonyl)-D-fructose ethylene glycol acetal as a yellow oil. ^{1}H NMR (400 MHz; $CDCl_3$): 5.08 (m, 1H), 4.82 (t, 1H), 4.13 (dd, 1H), 4.04 (m, 4H), 3.93 (dd, 1H), 3.87 (d, 1H), 3.81 (d, 1H), 3.13 (s, 3H).

Example 56

[0363] 1,4:3,6-dianhydro-2-deoxy-2-methylidene-D-*arabino*-hexitol: To a solution of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-5-*O*-(phenylcarbonyl)-D-*arabino*-hexitol (329mg, 1.34 mmol) in methanol (10mL) was added 50% aqueous sodium hydroxide (95mg, 1.19 mmol) and the mixture was stirred at room temperature for 30 minutes. Neutralization with 4M hydrogen chloride in 1,4-dioxane followed by concentration and column chromatography on silica (1:1 hexane/ethyl acetate) provided 141mg (74%) of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-D-*arabino*-hexitol as a colorless solid. ^{1}H NMR (400 MHz; $CDCl_3$): 5.37 (m, 1H), 5.20 (m, 1H), 4.80 (m, 1H), 4.54 (m, 2H), 4.43 (m, 1H), 4.26 (m, 1H), 3.95 (dd, 1H), 3.54 (dd, 1H), 2.70 (d, 1H).

[0364] 1,4:3,6-dianhydro-2-deoxy-2-methylidene-5-*O*-(methylsulfonyl)-D-*arabino*-hexitol: To a solution of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-D-*arabino*-hexitol (135mg, 0.95 mmol) and triethylamine (288mg, 2.85 mmol) in dichloromethane (10mL) was added methanesulfonyl chloride (222mg, 1.94 mmol) at 0°C under nitrogen. The solution was warmed to room temperature and stirred for 18 h. Dichloromethane (50mL) was added and the organic layer was washed with saturated aqueous sodium bicarbonate (2 x 25mL), water (25mL) and brine (25mL) then dried over anhydrous sodium sulfate. Filtration and concentration provided 213mg (72%) of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-5-*O*-(methylsulfonyl)-D-*arabino*-hexitol as a yellow oil. ^{1}H NMR (400 MHz; $CDCl_3$): 5.40 (m, 1H), 5.23 (m, 1H), 5.04 (m, 1H), 4.85 (m, 1H), 4.73 (t, 1H), 4.58 (m, 1H), 4.41 (m, 1H), 4.08 (dd, 1H), 3.86 (dd, 1H), 3.14 (s, 3H).

Example 57

[0365] 1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-*arabino*-hex-1-enitol: To a mixture of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-(D)-glycitol (4.32g, 17.3 mmol), triethylamine (4.91 mL, 35.3 mmol) and 4-dimethylaminopyridine (0.63g, 5.2 mmol) in dichloromethane (50 mL) at -10 ° to -15° was added trifluromethanesulfonic anhydride (3.48mL, 20.7 mmol) dropwise over ten minutes and the resulting mixture was stirred at this temperature for 3 hours. The mixture was poured into 100 mL of ice-water and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered then concentrated. The crude triflate was suspended in toluene (50 mL) followed by addition of 1,8-diazabicyclo[4,5,0]undec-7-ene (5.25 mL, 34.6 mmol) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was poured into ice-water and partitioned then the aqueous portion was extracted with dichloromethane (3 x 50 mL). The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flashed chromatography (silica gel, 5-20% ethyl acetate-hexane) to give 1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-*arabino*-hex-1-enitol, as a white solid, 3.10g, 77% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.08-8.06 (m, 2H), 7.61-7.57 (m, 1H), 7.56-7.43 (m, 2H), 6.62-6.61 (d, 1H), 5.48-5.46 (m,1H), 5.32-5.26 (m,1H), 5.13-5.10 (m, 2H), 4.18-4.14 (tr,1H), 3.61-3.56 (tr, 1H).

Example 58

[0366] Methyl 3,6-anhydro-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside: To a solution of 1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-arabino-hex-1-enitol (1.00g, 4.3 mmol) in methanol (17 mL) at -4°C was added 3-chloroperoxybenzoic acid (85%, 1.35g, 8.6 mmol), and the resulting mixture was slowly warmed to room temperature and stirred for 18 hours. The reaction mixture was concentrated, diluted with dichloromethane (50 mL), washed with saturated aqueous sodium bicarbonate solution, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (silica gel, 25-60% ethyl acetate-hexane) to give methyl 3,6-anhydro-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside as a white solid, 1.03g, 83% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.11-8.08 (d, 2H), 7.61-7.56 (tr, 1H), 7.48-7.44 (m, 2H), 5.24-5.17

(m, 2H), 4.96 (s, 1H), 4.57-4.56 (d, 1H), 4.27 (s, 1H), 4.22-4.18 (dd, 1H), 4.08-4.04 (dd, 1H) 3.36 (s, 3H).

[0367] Methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside: A mixture of methyl 3,6-anhydro-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside (1.03g, 3.7 mmol), silver (I) oxide (0.85g, 3.7 mmol) and methyl iodide (0.34 mL, 5.5 mmol) in DMF (2 mL) was heated at 60°C for 1 hour. After cooling to room temperature the reaction mixture was diluted with ethyl acetate (50 mL), filtered over celite, adsorbed on silica gel (10g) and purified by flash chromatography (silica gel, 5-30% ethyl acetate-hexane) to give methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside as a colorless oil, 0.82g, 76% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.11-8.09 (d, 2H), 7.60-7.56 (m, 1H), 7.46-7.44 (m, 2H), 5.24-5.20 (m, 1H), 5.18-5.09 (tr, 1H), 4.99 (s, 1H), 4.61-4.60 (d, 1H), 4.21-4.17 (tr, 1H), 4.08-4.03 (tr, 1H), 3.81 (s, 1H), 3.40 (s, 3H), 3.57 (s, 3H).

[0368] Methyl 3,6-anhydro-2-*O*-methyl-α-D-idofuranoside: A solution of methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside (820mg, 3.1mmol) and 50% sodium hydroxide (248 mg, 3.1 mmol) in methanol (10mL) was stirred at room temperature for 30 minutes. The material was adsorbed on silica gel (5g) and passed through a short column (15% ethyl acetate in hexanes to 5% methanol in ethyl acetate) to give methyl 3,6-anhydro-2-*O*-methyl-α-D-idofuranoside as a colorless oil, 420 mg, 85% yield. ^{1}H NMR (400MHz; $CDCl_3$): 5.04 (s, 1H), 5.84-5.81 (tr, 1H), 4.44-4.42 (tr, 1H), 4.25-4.19 (m, 1H), 3.85-3.75 (m, 1H), 3.49 (s, 3H), 3.43 (s, 3H), 2.75-2.72 (d, 1H).

[0369] Methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-β-L-glucofuranoside: Methyl 3,6-anhydro-2-*O*-methyl-α-D-idofuranoside (420 mg, 2.6 mmol) was dissolved in dichloromethane (10 mL) and pyridine (0.36 mL, 3.7 mmol) at 0°C. Methanesulfonyl chloride (0.14 mL, 3.1 mmol) was added and the resulting mixture was stirred at 0°C for 1 hour then at room temperature for 2 hours. The reaction mixture was washed with water and saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, filtered and concentrated to give methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-β-L-glucofuranoside as a colorless oil, 669mg, 95% yield, which was used without further purification.

Example 59

[0370] 3,6-anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose: A mixture of osmium tetroxide (4% in water, 0.25 mL, 0.03 mmol) and N-methylmorpholine (505 mg, 4.3 mmol) in 3 mL of 50% acetone in water was warmed to 60°C. A solution of 1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-*arabino*-hex-1-enitol (2.00g, 8.6 mmol) in 6 mL of 50% acetone in water was added over 3 hours. During this time an additional amount of N-methylmorpholine (1.01g, 8.6 mmol) was added in small portions periodically. Upon completion of the addition process the reaction was stirred for another hour and cooled to room temperature. The crude mixture was applied to a column of silica gel and flashed (0-6% methanol in 1:1 ethyl acetate:hexane) to give 3,6-anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose as a white solid, 1.5g, 65% yield. ^{1}H NMR (400MHz; DMSO-d_6): 8.01-7.95, (m, 2H), 7.68-7.66 (m, 1H), 7.57-7.53 (m, 2H), 5.18-5.11 (m, 2H), 4.85-4.81 (m, 1H, m), 4.37-4.35 (m, 1H), 4.05-3.96 (m, 2H), 3.85-3.83 (m, 1H).

[0371] 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-α-L-glucofuranoside: 3,6-Anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose (576 mg, 2.2 mmol) was added to a mixture of sodium hydride (60% oil dispersion, 346 mg, 8.7 mmol) and methyl iodide (0.54mL, 8.7 mmol) in 5 mL of DMF at 0°C and the resulting mixture was stirred for 1 hour. The reaction mixture was diluted with ethyl acetate and quenched with water (5 mL). The aqueous portion was extracted with ethyl acetate (3 x 5 mL). The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flashed chromatography (silica gel, 5-20% ethyl acetate in hexane) to give 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-α-L-glucofuranoside as a white solid, 270 mg, 42% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.09-8.07 (m, 2H), 7.61-7.57 (m, 1H), 7.48-7.27 (m, 2H), 5.25-5.22 (m, 1H), 5.07-5.06 (d, 1H), 4.94-4.91 (m, 1H), 4.73-4.71 (m, 1H), 4.20-4.16 (m, 1H), 3.96-3.94 (m, 1H), 3.85-3.83 (tr, 1H), 3.50 (s, 3H), 3.42 (s, 3H).

[0372] Methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-α-L-glucofuranoside: A solution of methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-α-L-glucofuranoside (230mg, 0.92 mmol) and 50% sodium hydroxide (74 mg, 0.92 mmol) in methanol (5 mL) was stirred at room temperature for 30 minutes. The mixture was adsorbed on silica gel (2g) and passed through a short column (15% ethyl acetate in hexanes to 5% methanol in ethyl acetate) to afford a colorless oil which was employed directly in the next step, 140

mg, 0.72 mmol, 95% yield. The alcohol was dissolved in dichloromethane (5 mL) and pyridine (121 μL, 1.03 mmol) was added at 0°C. Methanesulfonyl chloride (27μL, 0.88 mmol) was added and the resulting mixture was stirred at 0°C for 1 hour then at room temperature for 2 hours. The reaction mixture was washed with water and saturated aqueous sodium bicarbonate solution, dried over sodium sulfate, filtered and concentrated to give methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-α-L-glucofuranoside as a colorless oil, 190 mg, 96% yield.

Example 60

[0373] 3,6-Anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(phenylcarbonyl)-α-L-glucofuranose: A mixture of 3,6-anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose (1.00g), 2,2-dimethoxy propane (0.63 mL), p-toluenesulfonic acid (20 mg) and benzene (10 mL) was heated at reflux for 3 hours. The reaction mixture was cooled then adsorbed on silica gel (10g) and purified by flash chromatography (silica gel, 5-35% ethyl acetate in hexanes) to give 3,6-anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(phenylcarbonyl)-α-L-glucofuranose as colorless oil, 0.85g, 74% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.08-8.06 (d, 2H), 7.59-7.56 (tr, 1H), 7.46-7.42 (m, 2H), 5.99-5.98 (d, 1H), 5.35-5.31 (tr, 1H), 5.10-5.08 (d, 1H), 4.66-4.65 (d, 1H), 4.61-4.60 (d, 1H), 4.20-4.16 (dd, 1H), 3.91-3.74 (tr, 1H,), 1.50 (s, 3H), 1.34 (s, 3H).

[0374] 3,6-Anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(methylsulfonyl)-α-L-glucofuranose: A solution of 3,6-anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(phenylcarbonyl)-α-L-glucofuranose (850mg) and 50% sodium hydroxide (111 mg) in methanol (10mL) was stirred at room temperature for 30 minutes. The mixture was then adsorbed on silica gel (5g) and passed through a short column (15% ethyl acetate in hexanes to 5% methanol in ethyl acetate) and the alcohol intermediate, 390 mg, 70% yield, was used immediately in the next step. The alcohol was dissolved in dichloromethane (10 mL) and pyridine (0.32 mL) at 0°C. Methanesulfonyl chloride (0.12 mL) was added and the resulting mixture was stirred at 0°C for 1 hour then at room temperature for 2 hours. The reaction mixture was washed with water and saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, filtered and concentrated to give 3,6-anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(methylsulfonyl)-α-L-glucofuranose as a colorless oil, 485 mg, 90% yield, which was immediately employed in the next step.

Example 61

[0375] (3*S*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine: (*S*)-(+)-Prolinol (6.00 g, 59.3 mmol) was added to epichlorohydrin (47 mL, 600 mmol) at 0°C. The solution was stirred at 40°C for 0.5 h and then concentrated *in vacuo*. The residual oil was cooled in an ice bath and concentrated sulfuric acid (18 mL) was added dropwise with stirring. The mixture was heated at 170-180°C for 1.5 h, poured into ice (300 mL) and then basified with sodium carbonate to pH~8. The mixture was partitioned with ethyl acetate/hexanes and filtered. The filtrate was separated and the aqueous portion was extracted twice with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford oil that was purified by column chromatography (ethyl acetate for less polar product and then 30% methanol in ethyl acetate). (3*S*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (less polar product) (1.87 g, 10.7 mmol, 18% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 4.06 (dd, 1H), 3.79-3.71 (m, 1H), 3.60-3.48 (m, 2H), 3.36 (dd, 1H), 3.15 (dd, 1H), 3.13-3.06 (m, 1H), 2.21-2.01 (m, 3H), 1.90-1.68 (m, 3H), 1.39-1.24 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 (MH^+). (3*R*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (1.54 g, 8.77 mmol, 15% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 3.94-3.77 (m, 4H), 3.55 (dd, 1H), 3.02-2.93 (m, 2H), 2.45 (dd, 1H), 2.29-2.15 (m, 2H), 1.88-1.64 (m, 3H), 1.49-1.38 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 (MH^+).

[0376] Using the same or analogous synthetic techniques and/or substituting with alternative starting materials, the following were prepared:

[0377] (3*R*,8a*R*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine: ^{1}H NMR (400 MHz, $CDCl_3$): 4.05 (dd, 1H), 3.79-3.70 (m, 1H), 3.61-3.48 (m, 2H), 3.35 (dd, 1H), 3.15 (dd, 1H), 3.13-3.07 (m, 1H), 2.21-2.01 (m, 3H), 1.89-1.67 (m, 3H), 1.39-1.25 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 (MH^+).

[0378] (3*S*,8a*R*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine: ^{1}H NMR (400 MHz, $CDCl_3$): 3.93-3.77 (m, 4H), 3.55 (dd, 1H), 3.02-2.93 (m, 2H), 2.45 (dd, 1H), 2.30-2.15 (m, 2H), 1.88-1.64 (m, 3H), 1.49-1.37 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 (MH^+).

Example 62

[0379] (3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl acetate: (3*S*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (2.30 g, 13.1 mmol) and potassium acetate (12.8 g, 131 mmol) were stirred in dimethylformamide (25 mL) at 140°C for 20 h. The mixture was partitioned between ethyl acetate and water. The organic portion was washed twice with water, then with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl acetate as a brown oil (2.53 g, 12.7 mmol, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 4.14-4.02 (m, 3H), 3.81-3.72 (m, 1H), 3.37-3.31 (m, 1H), 3.09 (dt, 1H), 3.00 (dd, 1H), 2.21-2.00 (m, 3H), 2.10 (s, 3H), 1.90-1.67 (m, 3H), 1.39-1.24 (m, 1H); MS (EI) for $C_{10}H_{17}NO_3$: 200 (MH^+).

[0380] (3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethanol: (3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl acetate (2.36 g, 11.9 mmol) was treated with sodium methoxide (25 wt% solution in methanol; 2.7 mL) for 0.5 h. The mixture was cooled in an ice bath and a solution of 4M HCl in 1,4-dioxane (3 mL, 12.0 mmol) was added slowly. The mixture was stirred at room temperature for 5 minutes and then was concentrated *in vacuo* to afford a suspension which was diluted with dichloromethane, filtered and the filtrate was concentrated *in vacuo* to afford (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethanol as a brown oil (1.93 g, >100% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 4.05 (dd, 1H), 3.73-3.65 (m, 2H), 3.62-3.56 (m, 1H), 3.39-3.34 (m, 1H), 3.10 (dt, 1H), 3.00-2.95 (m, 1H), 2.24-1.98 (m, 4H), 1.97-1.70 (m, 3H), 1.44-1.28 (m, 1H); MS (EI) for $C_8H_{15}NO_2$: 158 (MH^+).

[0381] (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl methanesulfonate: (3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethanol (1.00 g, 6.37 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (2.4 mL, 17.3 mmol) was added at 0°C followed by dropwise addition of methanesulfonyl chloride (0.93 mL, 12.0 mmol). The solution was warmed to room temperature and stirred for 1.25 h and then was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic portion was washed with saturated sodium bicarbonate solution. The combined aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-

ylmethyl methanesulfonate as an orange-brown oil (1.20 g, 5.1 mmol, 80% yield). MS (EI) for $C_9H_{17}NO_4S$: 236 (MH^+).

Example 63

[0382] Octahydro-2*H*-quinolizin-3-ylmethanol: Ethyl octahydro-2*H*-quinolizine-3-carboxylate (2.35 g, 11.1 mmol) was added dropwise to a stirred suspension of lithium aluminum hydride (1 M solution in tetrahydrofuran, 33 mL, 33 mmol) in tetrahydrofuran (50 mL) at 0°C. The reaction was stirred at room temperature for 3 h. The mixture was cooled in an ice bath and ethyl acetate (6 mL) was added slowly, followed by water (1.25 mL), 15% aqueous sodium hydroxide solution (5 mL) and water (1.25 mL). The mixture was filtered through a pad of celite and washed with ether. The filtrate was concentrated *in vacuo* and dried rigorously to afford octahydro-2*H*-quinolizin-3-ylmethanol as a yellow oil (1.66 g, 9.82 mmol, 88% yield). MS (EI) for $C_{10}H_{19}NO$: 170 (MH^+).

[0383] Octahydro-2*H*-quinolizin-3-ylmethyl methanesulfonate: Octahydro-2*H*-quinolizin-3-ylmethanol (600 mg, 3.55 mmol) was dissolved in dichloromethane (8 mL) and triethylamine (1.5 mL, 10.8 mmol) was added at 0°C followed by dropwise addition of methanesulfonyl chloride (0.56 mL, 7.16 mmol). The solution was warmed to room temperature and stirred for 1.25 h and then was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford octahydro-2*H*-quinolizin-3-ylmethyl methanesulfonate as an orange oil (796 mg, 3.22 mmol, 91% yield). MS (EI) for $C_{11}H_{21}NO_3S$: 248 (MH^+).

Example 64

[0384] (3*S*,8a*S*)-3-(Hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one: A solution of methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate (3.50 g, 10.4 mmol) in methanol was added to 5% palladium on carbon (50 wt.% in water) in methanol and treated with hydrogen at 40 psi for 1 h. The mixture was filtered and the filtrate was brought to reflux briefly and then cooled and concentrated *in vacuo* to afford (3*S*,8a*S*)-3-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as

a colorless solid (1.50 g, 8.83 mmol, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.28-7.22 (m, 1H), 3.83-3.75 (m, 1H), 3.69 (dd, 1H), 3.56 (dd, 1H), 3.31 (t, 1H), 3.08 (dd, 1H), 2.92 (dt, 1H), 2.76-2.70 (m, 1H), 2.66 (dd, 1H), 2.28-2.16 (m, 1H), 2.02-1.73 (m, 3H); MS (EI) for $C_8H_{14}N_2O_2$: 171 (MH^+).

[0385] (3*S*,8a*S*)-3-({[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydro-pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one: To a solution of (3*S*,8a*S*)-3-(hydroxymethyl) hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (1.49 g, 8.82 mmol) in dimethylformamide (20 mL) was added triethylamine (2.45 mL, 17.6 mmol) and 4-dimethylaminopyridine (90 mg, 0.882 mmol). The solution was cooled in an ice bath and *tert*-butyldimethylsilyl chloride (2.66 g, 17.6 mmol) was added. The mixture was warmed to room temperature and stirred for 14 h. The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and water. The aqueous portion was extracted twice with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a pale brown solid which was triturated with ethyl acetate to afford (3*S*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl) hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as an off-white solid (1.74 g, 5.84 mmol, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 6.09-5.90 (m, 1H), 3.86-3.76 (m, 1H), 3.63 (dd, 1H), 3.44 (dd, 1H), 3.25 (t, 1H), 3.10 (ddd, 1H), 2.98-2.90 (m, 1H), 2.68-2.60 (m, 1H), 2.52 (dd, 1H), 2.28-2.18 (m, 1H), 2.06-1.95 (m, 1H), 1.93-1.74 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H); MS (EI) for $C_{14}H_{28}N_2O_2Si$: 285 (MH^+).

[0386] (3*S*,8a*S*)-3-({[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}methyl)-2-methylhexahydro pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one: (3*S*,8a*S*)-3-({[(1,1-Dimethylethyl)(dimethyl)silyl]oxy} methyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (1.51g, 5.32mmol) in dimethylformamide (8 mL) was added to an ice-cooled suspension of sodium hydride (60 wt.% dispersion in oil; 213 mg, 5.32 mmol) in dimethylformamide (8 mL). The mixture was stirred at 0°C for 0.25 h and then iodomethane (0.332 mL, 5.32 mmol) was added dropwise. The mixture was stirred at room temperature for 0.5 h and then was stirred at 70°C for 2 h. The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and water. The aqueous portion was extracted with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (3*S*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as a yellow oil (1.552 g, 5.21 mmol) which was dissolved in tetrahydrofuran (20 mL) and treated with tetrabutylammonium

fluoride (1.0M solution in tetrahydrofuran; 10.4 mL, 10.4 mmol) for 2 h at room temperature. The mixture was concentrated *in vacuo* and purified by column chromatography (10% methanol in dichloromethane) to afford (3*S*,8a*S*)-3-(hydroxymethyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as a yellow oil (496mg, 2.70mmol, 51% yield from (3*S*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy} methyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one). ^{1}H NMR (400 MHz, $CDCl_3$): 3.98-3.93 (m, 1H), 3.86 (dd, 1H), 3.61-3.55 (m, 1H), 3.29-3.25 (m, 1H), 3.09-3.03 (m, 1H), 3.03-2.97 (m, 1H), 3.02 (s, 3H), 2.93 (dd, 1H), 2.87-2.79 (m, 1H), 2.32-2.21 (m, 1H), 2.00-1.86 (m, 2H), 1.83-1.64 (m, 1H); MS (EI) for $C_9H_{16}N_2O_2$: 185 (MH^+).

Example 65

[0387] 1,2-Dideoxy-1-[(2*S*)-2-(methoxycarbonyl)-1-pyrrolidinyl]-2-[[(phenylmethoxy) carbonyl]amino]-D-*glycero*-hexitol: To a solution of 2-deoxy-2-{[(phenylmethyloxy) carbonyl]amino}-D-glycero-hexopyranose (5.0 g, 0.016 mol) in methanol (500 mL) was added L-proline methyl ester hydrochloride (2.8 g, 0.022 mol) and sodium cyanoborohydride (3.4 g, 0.054 mol). The solution was heated to 64 °C for 14 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* to afford 1,2-dideoxy-1-[(2*S*)-2-(methoxycarbonyl)-1-pyrrolidinyl]-2-[[(phenylmethoxy)carbonyl] amino]-D-*glycero*-hexitol (6.81 g, 100%) as a clear and colorless oil. MS (EI) for $C_{20}H_{31}N_2O_8$: 427 (MH^+).

Example 66

[0388] Methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate: 1,2-dideoxy-1-[(2*S*)-2-(methoxycarbonyl)-1-pyrrolidinyl]-2-[[(phenylmethoxy) carbonyl]amino]-D-*glycero*-hexitol (6.81 g, 0.016 mol) was taken into water (100 mL) and the resulting solution was cooled to 0°C. Sodium periodiate (14.8 g, 0.069 mol) dissolved in water was added dropwise and the resulting mixture was stirred at 0°C for 2 h. The reaction mixture was partitioned with dichloromethane (3x100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was taken up in methanol (200 mL) and the resulting solution was cooled to 0°C. Sodium borohydride

(1.98 g, 0.052 mol) was added and the reaction mixture was stirred for 1 h at 0°C. The reaction mixture was concentrated *in vacuo* and partitioned with dichloromethane and saturated aqueous ammonium chloride. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (5% methanol in dichloromethane) to yield methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate (4.9 g, 92%) as a white solid. MS (EI) for $C_{17}H_{25}N_2O_5$: 337 (MH^+).

[0389] Methyl 1-[(2*S*)-3-[(methylsulfonyl)oxy]-2-({[(phenylmethyl)oxy]carbonyl}amino) propyl]-L-prolinate: Methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino) propyl]-L-prolinate (200 mg, 0.594 mmol) was dissolved in dichloromethane (5 mL) followed by the addition of 4-(dimethylamino)pyridine (3.6 mg, 0.039 mmol) and triethylamine (0.125 mL, 0.891 mmol) and the resulting mixture was cooled to 0 °C. Methanesulfonyl chloride (0.060 mL, 0.773 mmol) was added dropwise and the reaction mixture was stirred for 1 h at 0°C. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford methyl 1-[(2*S*)-3-[(methylsulfonyl)oxy]-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate (246 mg, 100%) as a clear and colorless oil. MS (EI) for $C_{18}H_{27}N_2O_7S$: 415 (MH^+).

Example 67

[0390] 1,1-Dimethylethyl (3a*R*,6a*S*)-5-(hydroxymethyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate: Under a nitrogen atmosphere, borane tetrahydrofuran complex (1M in THF, 42 mL, 41.9 mmol) was diluted with tetrahydrofuran (42 mL) and cooled with an ice bath. Neat 2,3-dimethylbut-2-ene (5.0 mL, 41.9 mmol) was added in portions over 0.25 h and the solution was stirred at 0°C for 3 h. A solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-methylidenehexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate (1.98 g, 8.88 mmol) in tetrahydrofuran (10 mL) was added slowly, and the solution was warmed to room temperature and stirred 12 h. After cooling to 0°C, 10% aqueous sodium hydroxide (17 mL, 41.7 mmol) was added slowly, followed by 30% aqueous hydrogen peroxide (13 mL, 128 mmol) and the solution was warmed to room temperature. The solvent was removed *in vacuo* and the solution was partitioned between water and diethyl ether. The layers were separated and the aqueous layer was further extracted (3 x 50 mL diethyl ether). The

combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide 2.04 (95%) of 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxymethyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate, which was used without purification. ^{1}H NMR (400 MHz, $CDCl_3$): 8.50 (broad s, 1H), 3.66-3.46 (m, 3H), 3.20-3.00 (m, 2H), 2.70-2.59 (m, 2H), 2.37-2.18 (m, 1H), 2.04 (m, 1H), 1.84 (broad s, 1H), 1.70-1.55 (m, 1H), 1.46 (s, 9H), 1.17 (m, 1H), 0.93 (m, 1H).

[0391] 1,1-Dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]methyl}hexahydrocyclopenta [*c*]pyrrole-2(1*H*)-carboxylate: Methanesulfonyl chloride (0.2mL, 2.48mmol), was added dropwise to a solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxymethyl)hexahydro cyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.40 g, 1.65 mmol) and triethylamine (0.69 mL, 4.95 mmol) in 20 mL dichloromethane at 0°C and the reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated, the resulting crude mixture was diluted with 100 mL ethyl acetate and washed with water (30 mL), 1M aqueous sodium hydroxide, brine, 1M aqueous hydrochloric acid and brine again. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting 1,1-dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]methyl}hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate was used without further purification. MS (EI) for $C_{14}H_{25}NO_5S$: 320 (MH^+), 264 (M-tBu).

Example 68

[0392] 1,1-Dimethylethyl (3a*R*,6a*S*)-5-(hydroxy)-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate: Sodium borohydride (0.15 g, 4.00 mmol), was added to a solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-oxo-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.45 g, 2.00 mmol) in 10 mL methanol at 0°C and the reaction mixture was stirred for 1 h at this temperature. The solvent was evaporated, the crude mixture was diluted with 100 mL ethyl acetate and washed with water (30 mL), 1M aqueous hydrochloric acid and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxy)-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.44g, 98%). ^{1}H NMR (400 MHz, d_6-DMSO): 4.08 (m, 1H), 3.40 (m, 2H), 3.30 (m, 2H), 2.50 (m, 2H), 1.98 (m, 2H), 1.40 (s, 9H), 1.30 (m, 2H). MS (EI) for $C_{12}H_{21}NO_3$: 228 (MH^+).

[0393] 1,1-Dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]}hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate: Methanesulfonyl chloride (0.18 mL, 2.33 mmol), was added dropwise to a solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxy)-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.44 g, 1.94 mmol) and triethylamine (0.81 mL, 5.81 mmol) in 10 mL dichloromethane at 0°C and the reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated, the resulting crude mixture was diluted with 100 mL ethyl acetate and washed with water (30 mL), brine, 1M aqueous hydrochloric acid and brine again. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude 1,1-dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]}hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate was used without further purification. MS (EI) for $C_{13}H_{23}NO_5S$: 306 (MH^+).

Example 69

[0394] 3-(Chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine: A solution of (3*R*)-morpholin-3-ylmethanol (4.21 g, 36.0 mmol) in 2-(chloromethyl)oxirane (28.2 mL, 0.360 mol) was heated to 40°C for 3 h and then the solution was concentrated *in vacuo*. The intermediate was cooled in an ice bath and treated with 30.0 mL of concentrated sulfuric acid. The mixture was heated to 170°C for 2 h and then allowed to cool to room temperature. The mixture was poured into ice-water and solid sodium bicarbonate was carefully added until the solution was basic. 10% methanol in ethyl acetate was added and the biphasic mixture was filtered. The layers were separated and the aqueous layer was extracted (3 x 100 mL 10% methanol in ethyl acetate). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (SiO_2, 2:5 hexanes:ethyl acetate) provided 3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine 2.44g (35%) as two separated diastereomers. (3*R*,9a*S*)-3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine: (0.886 g, 13% yield): ^1H NMR (400 MHz, $CDCl_3$): 3.91 (m, 3H), 3.82 (m, 1H), 3.68 (dt, 1H), 3.61 (dd, 1H), 3.47 (dd, 1H), 3.35 (t, 1H), 3.19 (t, 1H), 2.80 (d, 1H), 2.54 (m, 2H), 2.40 (m, 2H); MS (EI) for $C_8H_{14}NO_2Cl$: 192 (MH^+). (3*S*,9a*S*)-3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine: (1.55 g, 22% yield): ^1H NMR (400 MHz, $CDCl_3$): 3.85 (m, 2H), 3.73 (m, 3H), 3.50 (m, 2H), 3.29 (t, 1H), 3.18 (t, 1H), 2.85 (dd, 1H), 2.64 (dd, 1H), 2.40 (m, 2H), 2.17 (t, 1H); MS (EI) for $C_8H_{14}NO_2Cl$: 192 (MH^+).

[0395] Hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate: A suspension of (3*R*,9a*S*)-3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine (1.97 g, 10.3 mmol) and potassium acetate (10.1 g, 102 mmol) in DMF (20.0 mL) was stirred at 140°C for 16 h, and then at 150°C for another 12 h. The reaction mixture was partitioned between water (250 mL) and ethyl acetate (250 mL), the organic layer was washed with 5% lithium chloride (2 x 100 mL) and brine (100 mL) then dried over anhydrous sodium sulfate and concentrated *in vacuo*. Column chromatography (SiO_2, 1:1 hexane:ethyl acetate, then 100% ethyl acetate) afforded 0.92 g (42%) of hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate as a yellow oil. Distinct diastereomers as described above were converted in this step to give: (3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate: ^{1}H NMR (400 MHz, $CDCl_3$): 4.18 (dd, 1H), 4.00 (m, 1H), 3.80 (dd, 1H), 3.68 (dt, 1H), 3.60 (dd, 1H), 3.46 (m, 2H), 3.22 (t, 1H), 2.64 (dd, 1H), 2.53 (m, 2H), 2.43-2.35 (m, 2H), 2.10 (s, 3H), and (3*S*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate: ^{1}H NMR (400 MHz, $CDCl_3$): 4.09 (d, 2H), 3.90-3.82 (m, 2H), 3.75-3.64 (m, 3H), 3.27 (t, 1H), 3.18 (t, 1H), 2.69 (dd, 1H), 2.63 (m, 1H), 2.46-2.33 (m, 2H), 2.16 (t, 1H), 2.10 (s, 3H).

[0396] (3*R*,9a*S*)-Hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl methanesulfonate: To a solution of (3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate (0.922 g, 4.28 mmol) in methanol (14.0 mL) was added 1.03 mL (4.50 mmol) of sodium methoxide (25% wt. in methanol) dropwise at room temperature. After 5 min., 1.6 mL (6.43 mmol) of 4.0M hydrogen chloride in dioxane was added and a pink precipitate formed. The solution was concentrated *in vacuo* and the pink solid was taken up in 30.0 mL dichloromethane. This slurry was cooled in an ice bath and triethylamine (3.0 mL, 21.5 mmol) was added, followed by methanesulfonyl chloride (0.37 mL, 4.71 mmol). The resultant yellow solution was stirred for 30 minutes at room temperature. The mixture was then partitioned between dichloromethane and saturated aqueous sodium bicarbonate then the aqueous layer was extracted (3 x 50 mL dichloromethane). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide crude (3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl methanesulfonate which was taken on to the following reaction without purification.

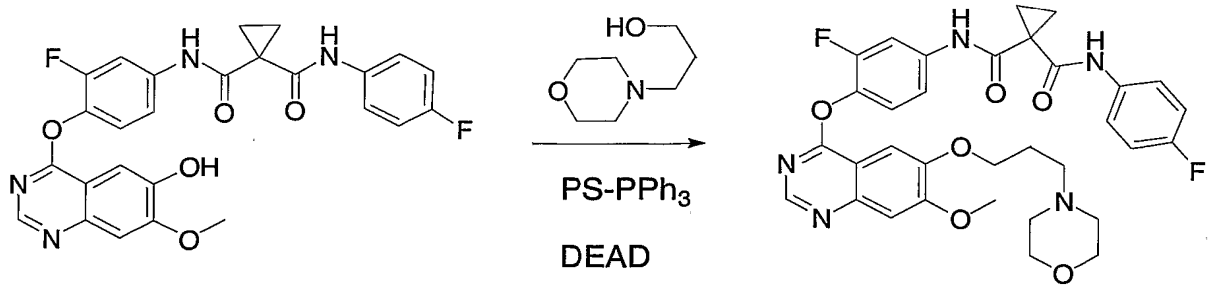
Example 70

[0397] (8a*R*)-6-(Chloromethyl)tetrahydro-1*H*-[1,3]thiazolo[4,3-*c*][1,4]oxazine: A solution of (4*R*)-1,3-thiazolidin-4-ylmethanol (0.300 g, 2.52 mmol) in 2-(chloromethyl)oxirane (2.0 mL, 25.5 mmol) was heated under nitrogen to 40°C for 12 h. The solution was then cooled to room temperature and 2-(chloromethyl)oxirane was removed *in vacuo*. The crude intermediate was cooled in ice, and was taken up in 2.0 mL of concentrated sulfuric acid. The resulting mixture was heated to 200°C for 0.5 h then poured carefully onto wet ice, which was allowed to melt. The aqueous solution was carefully made basic using solid sodium bicarbonate and the resulting mixture was filtered using water and 10% methanol in ethyl acetate as eluent. The layers were separated and the aqueous layer was extracted with 10% methanol in ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give 11.6 mg (2.4% yield) of crude (8a*R*)-6-(chloromethyl)tetrahydro-1*H*-[1,3]thiazolo[4,3-*c*][1,4]oxazine as a mixture of diastereomers which was directly taken on to the next step.

Example 71

[0398] 1,1-Dimethylethyl (3-*endo*)-3-{2-[(methylsulfonyl)oxy]ethyl}-8-azabicyclo[3.2.1]octane-8-carboxylate: To a solution of 1,1-dimethylethyl (3-*endo*)-3-(2-hydroxyethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (30.3 mg, 1.19 mmol) in dichloromethane (4.0 mL), was added triethylamine (0.5 mL, 3.56 mmol) and the solution was cooled to 0°C under nitrogen. Methanesulfonyl chloride (0.11 mL, 1.42 mmol) was added slowly and mixture was allowed to warm to room temperature and stirred for 1h. The reaction mixture was partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (2 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide 35.1 mg (89%) of 1,1-dimethylethyl (3-*endo*)-3-{2-[(methylsulfonyl)oxy]ethyl}-8-azabicyclo[3.2.1]octane-8-carboxylate, which was carried forward for alkylation without purification.

Example 72



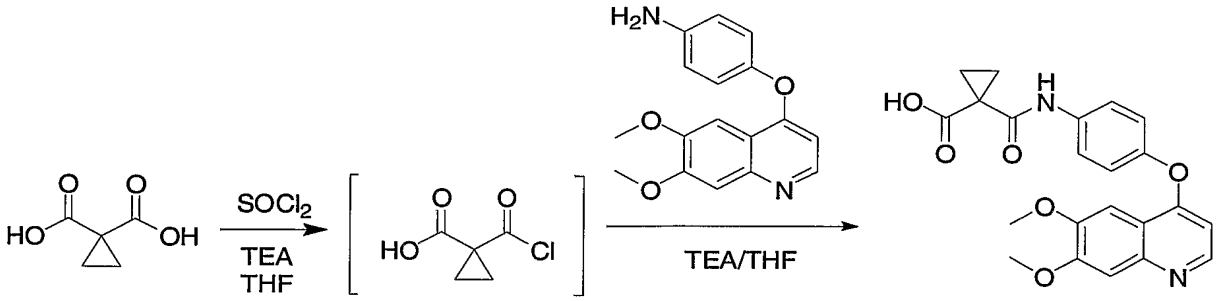
[0399] N-[3-Fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. Crude cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(6-hydroxy-7-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (333mg, 0.66mmol), PS-PPh_3 resin, (loading = 2.33mmol/g, 797mg, 1.86mmol), 3-morpholin-4-yl-propan-1-ol (0.26ml, 1.88mmol), and DEAD (0.31ml, 1.91mmol) were combined in CH_2Cl_2 (10ml) and stirred at room temperature for 1-2hrs. The reaction mixture was filtered and the resin thoroughly washed with CH_2Cl_2. The filtrate was concentrated *in vacuo* and the resulting residue was dissolved in EtOAc and washed with H_2O (4x) and sat'd NaCl (1x) and then extracted with 1N HCl (3x). The combined 1N HCl extractions were washed with EtOAc (2x). The acidic aqueous phase was then basified with 1N NaOH and extracted with EtOAc (3x). The combined EtOAc extractions were washed with H_2O (1x), sat'd NaCl (1x), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting residue was purified by preparative reverse phase HPLC (25mM NH_4OAc/acetonitrile) and the pure fractions were lyophilized to give cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[7-methoxy-6-(3-morpholin-4-yl-propoxy)-quinazolin-4-yloxy]-phenyl}-amide (4-fluoro-phenyl)-amide (42.6mg, 10%). 1HNMR (400MHz, DMSO-d6): d 10.37 (br s, 1H), 10.05 (br s, 1H), 8.55 (s, 1H), 7.84 (m, 1H), 7.65 (m, 2H), 7.58 (s, 1H), 7.43 (m, 3H), 7.16 (t, 2H), 4.27 (m, 2H), 4.00 (s, 3H), 3.60 (m, 6H), 2.39 (m, 4H), 1.99 (m, 2H), 1.47 (m, 4H). LC/MS Calcd for $[M+H]^+$ 634.2, found 634.1.

[0400] Using the same or analogous synthetic techniques and/or substituting with alternative starting materials, the following were prepared:

[0401] N-{3-fluoro-4-[(7-(methyloxy)-6-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide: ^1H NMR (400MHz, $CDCl_3$): δ 9.67 (s, 1H), 8.59 (s, 1H), 8.43 (s, 1H), 7.75 (d, 1H), 7.52 (s, 1H),

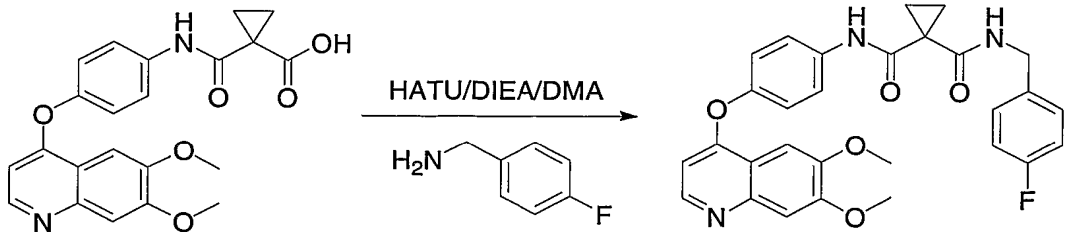
7.46 (m, 2H), 7.31 (s, 1H), 7.20 (m, 2H), 7.06 (t, 2H), 4.04 (d, 2H), 4.03 (s, 3H), 2.98 (d, 2H), 2.34 (s, 3H), 2.12-2.1.95 (m, 5H), 1.76 (m, 2H), 1.64 (m, 2H), 1.57 (m, 2H).

Example 73



[0402] Preparation of 1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropanecarboxylic acid. To the cyclopropyl di-carboxylic acid (449 mg, 3.45 mmol) in THF (3.5 mL) was added TEA (485 μL, 3.45 mmol). The resulting solution was stirred at room temperature under a nitrogen atmosphere for 40 minutes before adding thionyl chloride (250 μL, 3.44 mmol). The reaction was monitored by LCMS for the formation of mono acid chloride (quenched the sample with MeOH and looked for corresponding mono methyl ester). After 3 hours stirring at room temperature, 4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylamine (1.02 g, 3.44 mmol) was added as a solid, followed by more THF (1.5 mL). Continued to stir at room temperature for 16 hours. The resulting thick slurry was diluted with EtOAc (10 mL) and extracted with 1N NaOH. The biphasic slurry was filtered and the aqueous phase was acidified with conc. HCl to pH = 6 and filtered. Both solids were combined and washed with EtOAc, then dried under vacuum. The desired product, 1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropanecarboxylic acid, was obtained (962 mg, 68.7% yield, 97% pure) as a white solid. ^{1}H NMR (D_2O/NaOH): 7.97 (d, 1H), 7.18 (d, 2H), 6.76 (m, 4H), 6.08 (d, 1H), 3.73 (s, 3H), 3.56 (s, 3H), 1.15 (d, 4H).

Example 74



[0403] 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl] cyclopropane-1,1-dicarboxamide. To a solution of 1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropanecarboxylic acid (74.3 mg, 0.182 mmol), 4-Fluoro benzylamine (25 μL, 0.219 mmol), DIEA (90.0 μL, 0.544 mmol) in DMA (1.0 mL) was added HATU (203 mg, 0.534 mmol). The resulting solution was stirred at room temperature for 1 hour before adding dropwise to water (10 mL) with stirring. The slurry was sonicated, filtered and the solids were washed with 1 N NaOH followed by water. After air drying, the solids were further purified by prep HPLC, affording 'N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl]cyclopropane-1,1-dicarboxamide (33 mg, 35% yield, 98% pure) as a white solid. ^{1}H NMR (DMSO, d_6): 10.82 (s, 1H), 8.80 (d, 1H), 8.50 (t, 1H), 7.83 (d, 2H), 7.74 (s, 1H), 7.56 (s, 1H), 7.30-7.38 (m, 4H), 7.15 (t, 2H), 6.80 (d, 1H), 4.32 (d, 2H), 4.04 (s, 3H), 4.03 (s, 3H), 1.42 (s, 4H).

[0404] The following compounds were prepared, in a similar manner as above, from the coupling of 1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropane carboxylic acid with a corresponding alkylamine or arylamine.

[0405] N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.62 (s, 1H), 8.79 (d, 1H), 8.24 (t, 1H), 7.83 (d, 2H), 7.72 (s, 1H), 7.58 (s, 1H), 7.37 (d, 2H), 6.76 (d, 1H), 4.04 (s, 3H), 4.03 (s, 3H), 3.98 (m, 2H), 3.66 (m, 2H), 3.49 (m, 4H), 3.25 (t, 2H), 3.13 (br., 2H), 1.42 (d, 4H).

[0406] N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.78 (s, 1H), 10.53 (s, 1H), 8.43 (d, 1H), 8.12 (d, 1H), 7.82 (d, 2H), 7.49 (s, 1H), 7.37 (s, 1H), 7.20-7.28 (m, 3H), 7.15 (dd, 1H), 7.01 (td, 1H), 6.35 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.47 (s, 2H), 2.17 (br., 4H), 1.49 (m, 4H), 1.41 (m, 4H), 1.32 (br., 2H).

[0407] 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.98 (s, 1H), 10.56 (s, 1H), 8.42 (d, 1H), 8.10 (dd, 1H), 7.81 (m, 2H), 7.49 (s, 1H), 7.37 (s, 1H), 7.17-7.27 (m, 4H), 7.01 (td, 1H), 6.35 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.61 (s, 2H), 2.30 (br., 4H), 1.47 (br., 4H), 1.43 (m, 4H).

[0408] 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.12 (s, 1H),

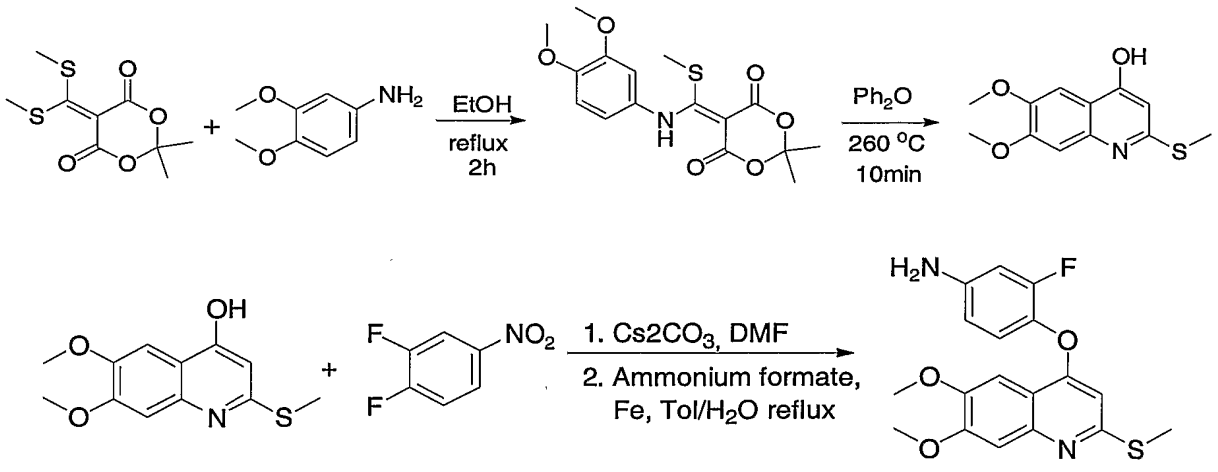
10.03 (s, 1H), 8.44 (d, 1H), 7.74 (d, 2H), 7.57 (s, 1H), 7.53 (d, 1H), 7.48 (s, 1H), 7.37 (s, 1H), 7.21 (m, 3H), 6.98 (d, 1H), 6.40 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.56 (t, 4H), 3.41 (s, 2H), 2.34 (br., 4H), 1.48 (s, 4H).

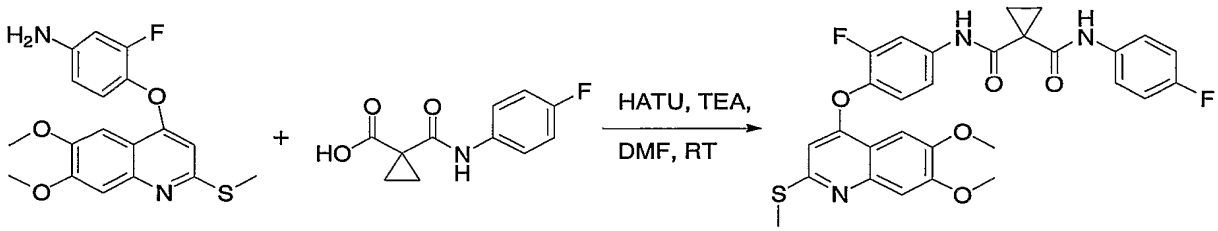
[0409] 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.54 (s, 1H), 10.47 (s, 1H), 8.43 (d, 1H), 8.08 (d, 1H), 7.78 (d, 2H), 7.49 (s, 1H), 7.37 (d, 1H), 7.18-7.30 (m, 4H), 7.03 (t, 1H), 6.37 (d, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.50 (s, 2H), 3.44 (br., 4H), 2.20 (br., 4H), 1.48 (d, 4H).

[0410] 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.0-10.2 (br., 2H), 8.46 (d, 1H), 7.76 (d, 2H), 7.53 (m, 3H), 7.39 (s, 1H), 7.24 (m, 3H), 6.98 (d, 1H), 6.43 (d, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.37 (s, 2H), 2.31 (br., 4H), 1.48 (m, 8H), 1.39 (br., 2H).

[0411] 'N-(4-{[6,7-Bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide. 1H NMR (DMSO-d6): 10.0-10.2 (br., 2H), 8.46 (d, 1H), 7.77 (d, 2H), 7.59 (s, 1H), 7.53 (d, 1H), 7.51 (s, 1H), 7.39 (s, 1H), 7.23 (m, 3H), 6.99 (d, 1H), 6.43 (d, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.52 (s, 2H), 2.42 (br., 4H), 1.69 (br, 4H), 1.48 (s, 4H).

Example 75





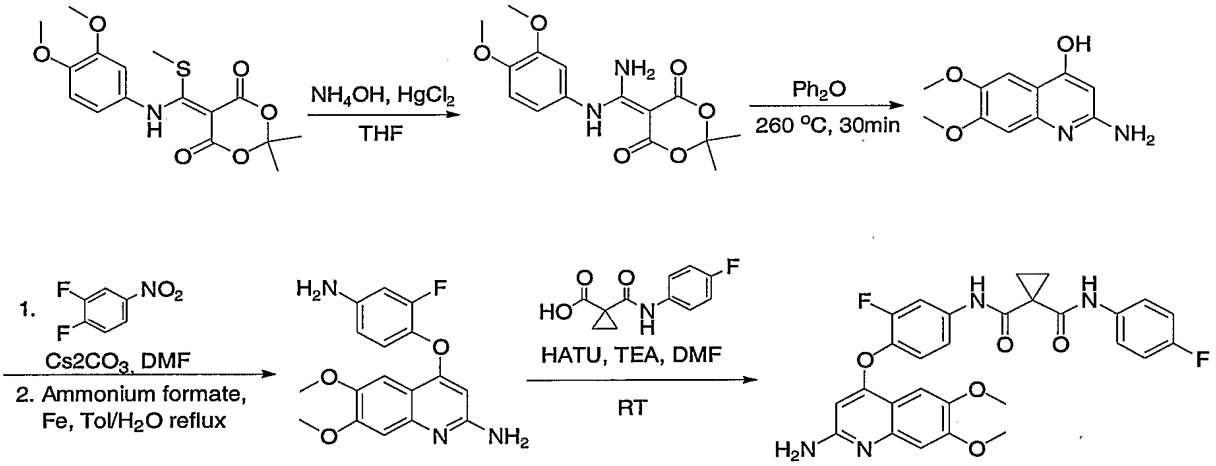
[0412] Synthesis of N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide Commercially available 5-(bis-methylsulfanyl-methylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione (3.5 g, 14 mmol) and 3,4-dimethoxyoaniline (2.2 g, 14 mmol) were reflux in EtOH (20 mL) for 2 hours. The EtOH was removed under reduced pressure and EtOAc was added to the residue. The product was filtered and washed with cold EtOAc (3X). 5-[(3,4-dimethoxy-phenylamino)-methylsulfanyl-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione was obtained as a white solid (1.7 g, 47% yield) and used without further purification. LCMS: m/z 352 $(M-H)^-$.

[0413] A mixture of 5-[(3,4-dimethoxy-phenylamino)-methylsulfanyl-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (1.7 g, 6.6 mmol) and diphenylether (3.5 g, 21 mmol) were heated at 260 ^{0}C for 10 minutes. The mixture was cooled to room temperature and heptane was added. 6,7-Dimethoxy-2-methylsulfanyl-quinolin-4-ol was filtered and isolated as an orange solid and used without further purification (1.4 g, 83% yield). LCMS: m/z 352 $(M+H)^+$.

[0414] A mixture of 6,7-dimethoxy-2-methylsulfanyl-quinolin-4-ol (1.0 g, 4.0 mmol), 3,4-difluoronitrobenzene (0.48 mL, 4.3 mmol), cesium carbonate (2.6 g, 8.0 mmol), and DMF (15 mL) was stirred at room temperature for 12 hours, after which time, the mixture was filtered. The filtrate was extracted with DCM, washed with 10% $LiCl_{(aq.)}$, water, (1X) and brine (1X), followed by drying over Na_2SO_4 and concentration *in vacuo*. The crude solids were purified by flash chromatography (silica gel, 5% MeOH in DCM), affording the nitroquinoline (1.3 g, 85.8% yield) as an orange solid. LCMS: m/z 391 $(M+H)^+$. A mixture of nitroquinoline (0.33 g, 0.85 mmol), 5% Pt/S on carbon (0.050 g), ammonium formate (0.40 g, 6.3 mmol) in EtOH (5 mL) was heated at 80 ^{0}C for 1 hour The mixture was cooled to room temperature and the solvent removed under reduced pressure. The residue was dissolved in DCM, the mixture filtered, and the precipitate discarded. Removal of the organic solvent afforded 4-(6,7-dimethoxy-2-methylsulfanyl-quinolin-4-yloxy)-3-fluoro-phenylamine as an orange oil (220 mg, 73% yield). LCMS: m/z 361 $(M+H)^+$.

[0415] To a mixture of 4-(6,7-dimethoxy-2-methylsulfanyl-quinolin-4-yloxy)-3-fluoro-phenylamine (0.22 g, 0.61 mmol) and 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (0.16 g, 0.73 mmol) in DMF (5 mL) was added TEA (0.25 mL, 1.8 mmol) followed by HATU (0.57 g, 1.5 mmol). The resulting solution was stirred overnight at room temperature. The reaction mixture was dumped into water and extracted with DCM (2X). The combined extracts were washed with 5% $LiCl_{(aq.)}$ (3X), water, (1X) and brine (1X), followed by drying over Na_2SO_4 and concentration *in vacuo*. The crude solids were purified by preparatory HPLC with ammonium acetate, affording N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (0.39 g, 11% yield) as a white solid. ^1H NMR (DMSO-d_6) δ 10.34 (s, 1H), 9.94 (s, 1H), 7.83 (d, 1H), 7.59 (m, 2H), 7.56 (m, 1H), 7.40 (m, 2H), 7.23 (s, 1H), 7.09 (t, 2H), 6.12 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.48 (s, 3H), 1.40 (m, 4H).

Example 76



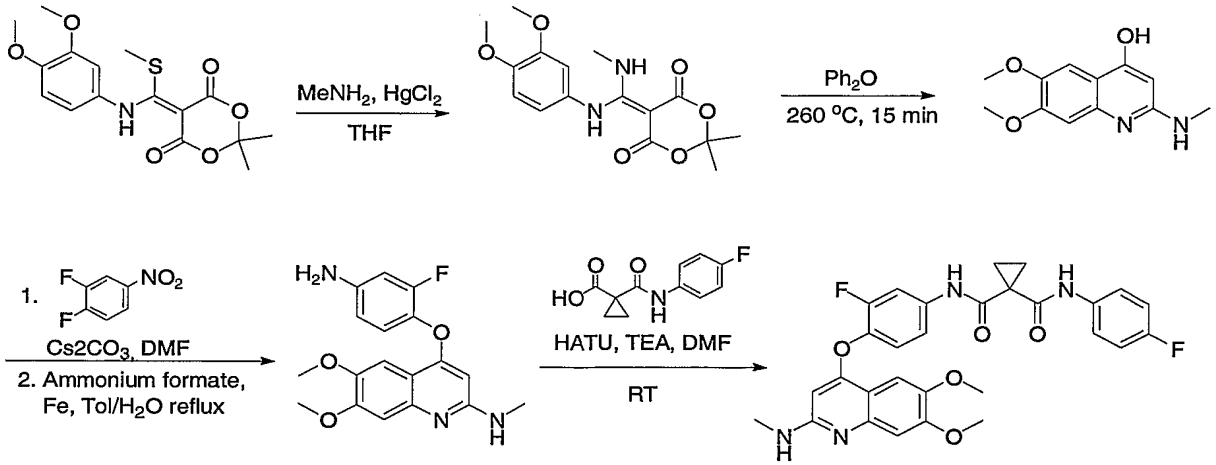
[0416] Synthesis of N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. A mixture of 5-[(3,4-dimethoxy-phenylamino)-methylsulfanyl-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (1.0 g, 2.8 mmol), 30% ammonium hydroxide (8.5 mL), $HgCl_2$ (0.76 g, 2.8 mmol) in THF (5 mL) was stirred at room temperature for 30 minutes. The mixture was extracted with DCM and water (3X) and dried with Na_2SO_4. Concentration *in vacuo* afforded 5-[amino-(3,4-dimethoxy-phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione as a white solid (0.90 g, 97% yield) and this compound was used without further purification. LCMS: m/z 321 $(M-H)^-$.

[0417] A mixture of 5-[amino-(3,4-dimethoxy-phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (0.90 g, 2.8 mmol) and diphenylether (3.0 g, 18 mmol) was heated at 260 ^{0}C for 30 minutes. The mixture was cooled to room temperature and heptane was added. Product 2-amino-6,7-dimethoxy-quinolin-4-ol was filtered and isolated as an orange solid and used without further purification (0.31 g, 33% yield). LCMS: m/z 221 $(M+H)^+$.

[0418] 4-(4-Amino-2-fluoro-phenoxy)-6,7-dimethoxy-quinolin-2-ylamine was synthesized from 2-amino-6,7-dimethoxy-quinolin-4-ol in a similar manner as 4-(6,7-dimethoxy-2-methylsulfanyl-quinolin-4-yloxy)-3-fluoro-phenylamine, and obtained as a white solid (4.0% yield). LCMS: m/z 330 $(M+H)^+$.

[0419] N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide was synthesized from 4-(4-amino-2-fluoro-phenoxy)-6,7-dimethoxy-quinolin-2-ylamine in a similar manner as N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. It was purified by preparatory HPLC using ammonium acetate and isolated as a white solid (4.0% yield). ^{1}H NMR (DMSO-d_6) δ 10.34 (s, 1H), 9.95 (s, 1H), 7.82 (d, 1H), 7.58 (m, 2H), 7.44 (d, 1H), 7.33 (t, 1H), 7.25 (s, 1H), 7.09 (t, 2H), 7.07 (s, 1H), 6.17 (br s, 2H), 5.66 (s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 1.40 (d, 4H). LCMS: m/z 535 $(M+H)^+$.

Example 77



[0420] Synthesis of 'N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. A mixture of 5-

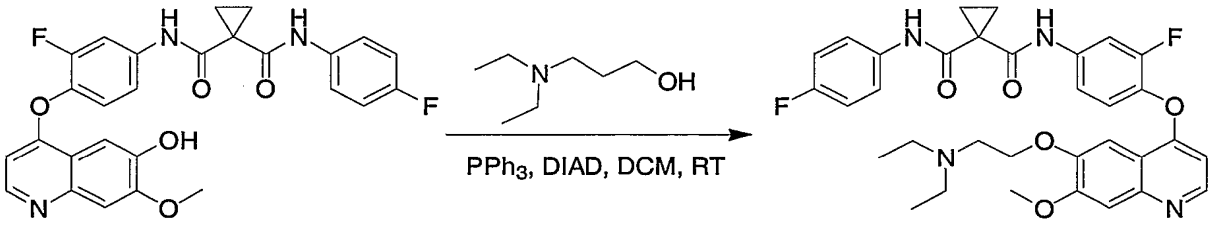
[(3,4-dimethoxy-phenylamino)-methylsulfanyl-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (0.50 g, 1.4 mmol), methylamine (2 M in THF, 0.75 mL, 1.5 mmol), $HgCl_2$ (0.38 g, 1.4 mmol) in THF (5 mL) was stirred at room temperature for 30 minutes. The mixture was extracted with DCM and water (3X) and dried with Na_2SO_4. Concentration *in vacuo* afforded 5-[(3,4-dimethoxy-phenylamino)-methylamino-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione as a yellow solid (0.48 g, 99% yield) and this compound was used without further purification. LCMS: m/z 335 $(M-H)^-$.

[0421] A mixture of 5-[(3,4-dimethoxy-phenylamino)-methylamino-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (0.40 g, 2.8 mmol) and diphenylether (3.0 g, 18 mmol) was heated at 260 ^{0}C for 15 minutes. The mixture was cooled to room temperature and heptane was added. Product 6,7-dimethoxy-2-methylamino-quinolin-4-ol was filtered and isolated as a tan solid and used without further purification (0.30 g, quantitative yield). LCMS: m/z 235 $(M+H)^+$.

[0422] [4-(4-Amino-2-fluoro-phenoxy)-6,7-dimethoxy-quinolin-2-yl]-methyl-amine was synthesized from 6,7-dimethoxy-2-methylamino-quinolin-4-ol in a similar manner as 4-(4-Amino-2-fluoro-phenoxy)-6,7-dimethoxy-quinolin-2-ylamine, and isolated as a yellow oil (58% yield). LCMS: m/z 330 $(M+H)^+$.

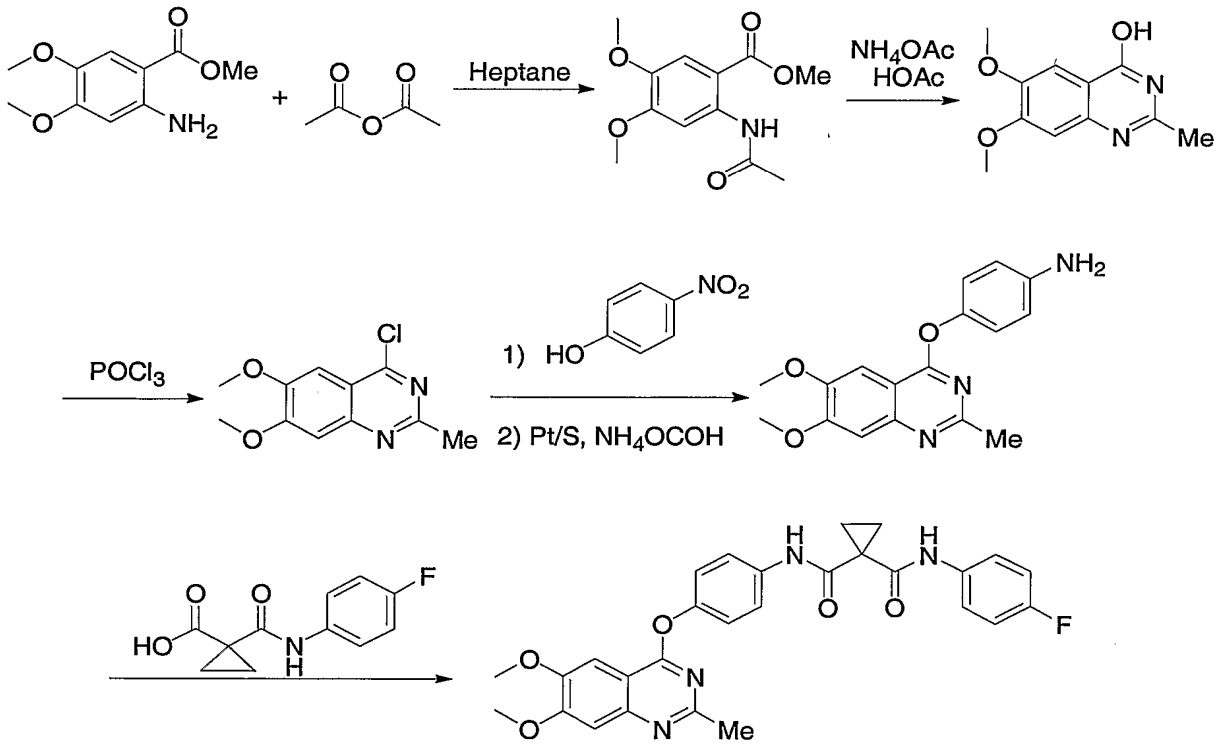
[0423] 'N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide was synthesized from [4-(4-amino-2-fluoro-phenoxy)-6,7-dimethoxy-quinolin-2-yl]-methyl-amine in a similar manner as N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluoro-phenyl)cyclopropane-1,1-dicarboxamide. It was purified by preparatory HPLC using ammonium acetate and isolated as a white solid (6.0 mg, 4.0% yield). ^{1}H NMR (DMSO-d_6) δ 10.42 (s, 1H), 9.91 (s, 1H), 7.88 (dd, 1H), 7.56 (m, 2H), 7.44 (m, 4H), 7.09 (t, 2H), 5.90 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.39 (br s, 1H), 2.92 (s, 3H), 1.41 (dt, 4H). LCMS: m/z 535 $(M+H)^+$.

Example 78



[0424] 'N-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a slurry of cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(6-hydroxy-7-methoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (0.12 g, 0.23 mmol), hydroxypropyldiethylamine (0.090 mL, 0.61 mmol), triphenylphosphine (0.20 g, 0.76 mmol) in DCM (10 mL) was added DIAD (0.17 mL, 0.86 mmol). The resulting mixture was stirred at room temperature for 12 hours, after which time, the solvent was removed under reduced pressure. The residue was extracted with EtOAc and 1N HCl (6X) and brine (1X) followed by drying with Na_2SO_4. Concentration of the organic fraction *in vacuo* afforded 'N-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as a yellow oil (0.18 g, wet, ca 95% purity by analytical HPLC). Further purification by preparatory HPLC using ammonium acetate afforded the product in 99% purity by analytical HPLC. LCMS: m/z 619 $(M+H)^+$. ^1H NMR (DMSO-d_6) δ 10.37 (br s, 1H), 10.00 (s, 1H), 8.44 (d, 1H), 7.87 (d, 1H), 7.62 (m, 2H), 7.49 (m, 2H), 7.41 (m, 2H), 7.13 (t, 2H), 6.40 (d, 1H), 4.17 (t, 2H), 3.93 (s, 3H), 2.59 (t, 2H), 2.49 (m, 6H), 1.91 (m, 4H), 0.94 (t, 6H).

Example 79



[0425] 'N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide. Commercially available 2-amino-4,5-dimethoxy-benzoic acid methyl ester (3g, 0.014 mol) and acetic anhydride (4.03 mL, 0.0426 mol) were heated in heptane at 100°C for 3 hours. After removal of heptane *in vaccuo*, the crude product of 2-acetylamino-4,5-dimethoxy-benzoic acid methyl ester was obtained and used without further purification. LC/MS: m/z 254 (M+H).

[0426] To the crude 2-acetylamino-4,5-dimethoxy-benzoic acid methyl ester obtained above was added ammonium acetate (7.98g, 0.104 mol) and acetic acid (10 mL). The mixture was heated at reflux in a pressure tube until the formation of the desired cyclization product, as indicated by LC/MS: m/z 221 (M+H). After cooling to RT, the reaction mixture was diluted with water, and extracted with EtOAc 3 times. The combined organic phase was basified with aq. NaOH solution, and washed 3 times with EtOAc. The aqueous layer was then acidified with aq. HCl and extracted three times with EtOAc. The combined organic extract was dired over Na_2SO_4 and concentrated in vacuo, affording 6,7-dimethoxy-2-methyl-quinazolin-4-ol (0.15g), which was used without further purification. LC/MS: m/z 221 (M+H).

[0427] A mixture of 6,7-dimethoxy-2-methyl-quinazolin-4-ol obtained from previous step (0.15g, 0.68 mmol) and POCl3 (1.59 mL, 17.04 mmol) was heated at reflux for 48 hours. The reaction mixture was poured into ice water, neutralized with $NaHCO_3$, and adjusted to basic with K_2CO_3. The mixture was cooled to 0°C with stirring. The resulting precipitate was filtered, giving 4-chloro-6,7-dimethoxy-2-methyl-quinazoline (0.094g), which was used without further purification.

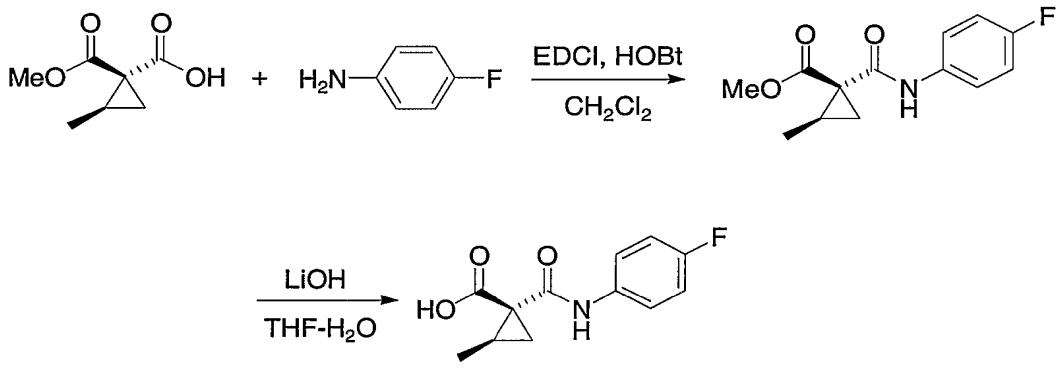
[0428] A mixture of the chloro quinazoline (0.094g, 0.397 mmol) obtained above, 4-nitrophenol (0.11g, 0.795 mmol) and bromobenzene (3mL) was heated at 160°C for 48 hours. The solvent was then removed and the reaction was taken up in MeOH. Et_2O was added and the reaction stirred 30 min and the precipitate was filtered, affording 6,7-dimethoxy-2-methyl-4-(4-nitro-phenoxy)-quinazoline (0.081g) as a very light yellow solid. LC/MS: m/z 342 (M+H).

[0429] A mixture of 6,7-dimethoxy-2-methyl-4-(4-nitro-phenoxy)-quinazoline (0.081g, 0.236 mmole), Pt/S (0.008g, 15 mol%), ammounium formate (0.098g, 1.56 mmol) and EtOH (3mL) was heated with stirring at 70°C for 3 hours. The reaction mixture was then filtered while hot and washed with hot EtOH. The crude product of 4-(6,7-dimethoxy-2-

methyl-quinazolin-4-yloxy)-phenylamine (0.924g) was obtained as a yellow solid, which was used in the next reaction without further purification. LC/MS: m/z 312 (M+H).

[0430] To a mixture of 4-(6,7-dimethoxy-2-methyl-quinazolin-4-yloxy)-phenylamine (0.100g, 0.321 mmol) and 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (0.056g, 0.386 mmol) in DMF was added DIEA (0.168 mL, 0.963 mmol), followed by HATU (0.183g, 0.482 mmol). The reaction mixture was stirred at RT for 15 hours. The mixture was diluted with EtOAc, washed with 5% LiCl aq solution three times, dried over Na2SO4, and concentrated *in vacuo*. The crude product was purified on preparative HPLC to give 'N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide (3.2 mg) as a white solid. 1H NMR (DMSO-d6) 10.15 (bs, 1H), 10.01 (bs, 1H), 7.69-7.75 (m, 2H), 7.61-7.68 (m, 2H), 7.52 (s, 1H), 7.32 (s, 1H), 7.23-7.29 (m, 2H), 7.12-7.19 (m, 2H), 3.93 (d, 6H), 2.43 (s, 3H), 1.53 (s, 4H).

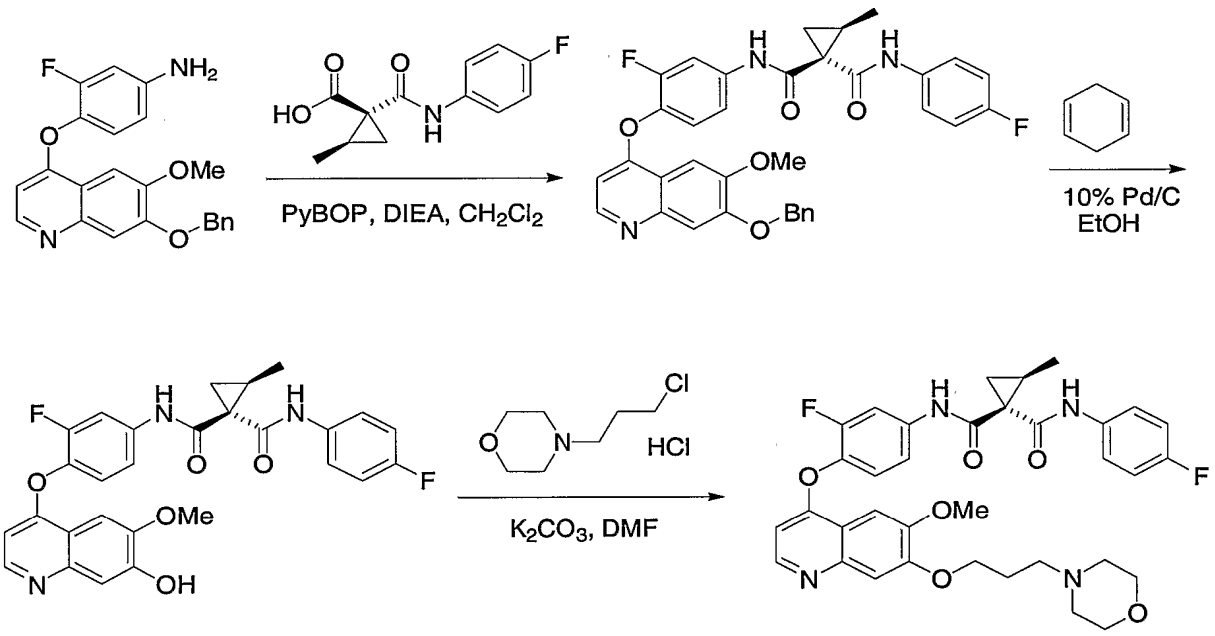
Example 80



[0431] Preparation of 1-(4-Fluoro-phenylcarbamoyl)-2-methyl-cyclopropanecarboxylic acid. 2-Methylcyclopropane-1,1-dicarboxylic acid methyl ester was prepared by following the literature procedure (Baldwin, J. E.; Adlington, R. M.; Rawlings, B. J. Tetrahedron Lett. 1985, 481.) The carboxylic acid (700 mg, 4.4 mmol) was dissolved in CH_2Cl_2 (10 mL). To the resulting solution was added 4-fluoroaniline (590 mg, 5.3 mmol), HOBt (890 mg, 6.6 mmol) and EDCI (2.5 g, 13.2 mmol). The stirring was continued for 3 h at rt. CH_2Cl_2 (30 mL) was added to the reaction mixture, and the resulting solution was washed with brine, and dried over Na_2SO_4. CH_2Cl_2 was removed under reduced pressure. Further purification by column chromatography gave 635 mg (57%) of the desired amide.

[0432] The methyl ester obtained above was then treated with $LiOH \cdot H_2O$ (116 mg, 2.78 mmol, 1.1 eqiv.) in THF (2 mL) and H_2O (1 mL) for 3h at rt. THF was removed under reduced pressure. The aqueous solution was diluted with 20 mL of H_2O, washed with ether (10 mL), and acidified with 1 N HCl. The solid was filtered, dissolved in EtOAc, and dried over Na_2SO_4. Removal of EtOAc gave the crude product of 1-(4-fluoro-phenylcarbamoyl)-2-methyl-cyclopropane-carboxylic acid, which was used in the next reaction. ^1H NMR (400 MHz, DMSO-d_6) δ 12.99 (br s, 1 H), 10.33 (br s, 1 H), 7.59 (dd, J = 9.0, 5.0 Hz, 2 H), 7.11 (dd, J = 9.0, 9.0 Hz, 2 H), 1.86-1.78 (m, 1 H), 1.43 (dd, J = 9.0, 4.2 Hz, 1 H), 1.30 (dd, J = 7.8, 4.3 Hz, 1 H), 1.19 (d, J = 6.3 Hz, 3 H).

Example 81



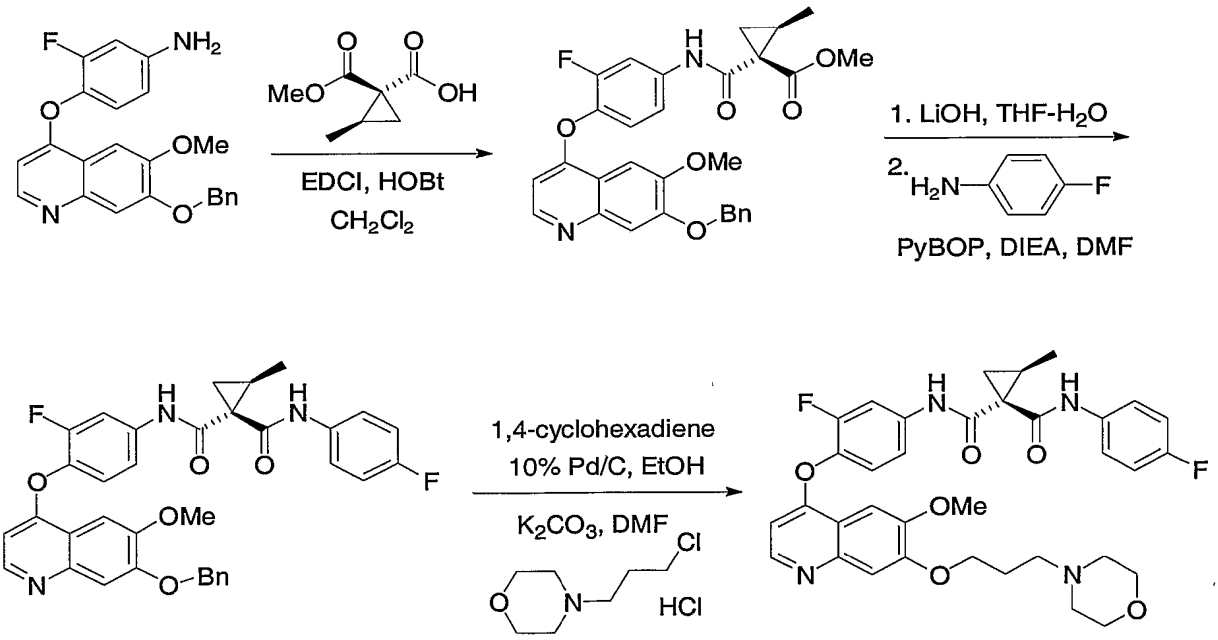
[0433] Synthesis of (1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl) oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide. To a solution of 4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenylamine (150 mg, 0.38 mmol) in CH_2Cl_2 (3 mL) was added DIEA (341 mg, 2.64 mmol), 1-(4-fluoro-phenylcarbamoyl)-2-methyl-cyclopropanecarboxylic acid (120 mg, 0.49 mmol) and PyBOP (686 mg, 1.32 mmol). The reaction mixture was stirred at rt for 6 h. After standard workup, the crude product was purified by column chromatography.

[0434] The coupling product (130 mg, 0.21 mmol) obtained above was dissolved in EtOH (2 mL). 1,4-cyclohexadiene (170 mg, 2.1 mmol) and 10% Pd/C (10 mg) were added. The

mixture was stirred for 2 h under reflux. After cooling, the mixture was filtered through Celite, and washed with MeOH. Removal of the solvents gave the crude product (136 mg), which was used in the next reaction.

[0435] To a solution of the 7-hydroxyquinoline (136 mg, 0.26 mmol) in DMF (2 mL) was added 4-(3-chloropropyl)morpholine hydrochloride (70 mg, 0.35 mmol) and K_2CO_3 (69 mg, 0.50 mmol). The reaction mixture was then stirred at 80 °C for 5 h. After cooling, EtOAc (20 mL) was added. The EtOAc solution was washed twice with brine, and dried over Na_2SO_4. Removal of EtOAc and purification by column chromatography (CH_2Cl_2 : MeOH = 10:1) gave '(1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide. The product was then dissolved in ethyl ether, and treated with 1.5 equiv. of 1 N HCl/ether. Filtration and lyophilization gave the HCl salt of '(1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (br s, 1 H), 10.26 (br s, 1 H), 10.15 (br s, 1 H), 8.74 (br s, 1 H), 7.95 (br d, J = 13.2 Hz, 1 H), 7.8-7.5 (m, 6 H), 7.16 (t, J = 8.9 Hz, 2 H), 6.82 (br s, 1 H), 4.34 (t, J = 5.9 Hz, 2 H), 4.02 (s, 3 H), 3.99 (br s, 2 H), 3.77 (br t, J = 12.0 Hz, 2 H), 3.56-3.30 (m, 4 H), 3.17-3.07 (m, 2 H), 2.40-2.30 (m, 2 H), 2.04-1.95 (m, 1 H), 1.45 (dd, J = 7.2, 4.7 Hz, 1 H), 1.36 (dd, J = 8.5, 4.5 Hz, 1 H), 1.09 (d, J = 6.2 Hz, 3 H).

Example 82



[0436] Synthesis of (1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]-quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide. To a solution of 4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenylamine (322 mg, 0.82 mmol) and 2-Methyl-cyclopropane-1,1-dicarboxylic acid methyl ester (195 mg, 1.23 mmol) in CH_2Cl_2 (4 mL) was added HOBt (61 mg, 0.32 mmol) and EDCI (211 mg, 1.64 mmol). The stirring was continued for 12 h at rt. The reaction mixture was then diluted with EtOAc and washed with brine. Removal of organic solvents *in vacuo* and further purification by column chromatography gave the desired coupling product (153 mg).

[0437] The product (153 mg, 0.29 mmol) obtained above was treated with $LiOH \cdot H_2O$ (15 mg, 0.35 mmol) in THF (1 mL) and H_2O (1 mL) for 2 h. THF was removed. 10 mL of H_2O was added to the mixture. The aqueous solution was washed with ether, and acidified with 1 N HCl. The solid was then filtered and dried under vacuum.

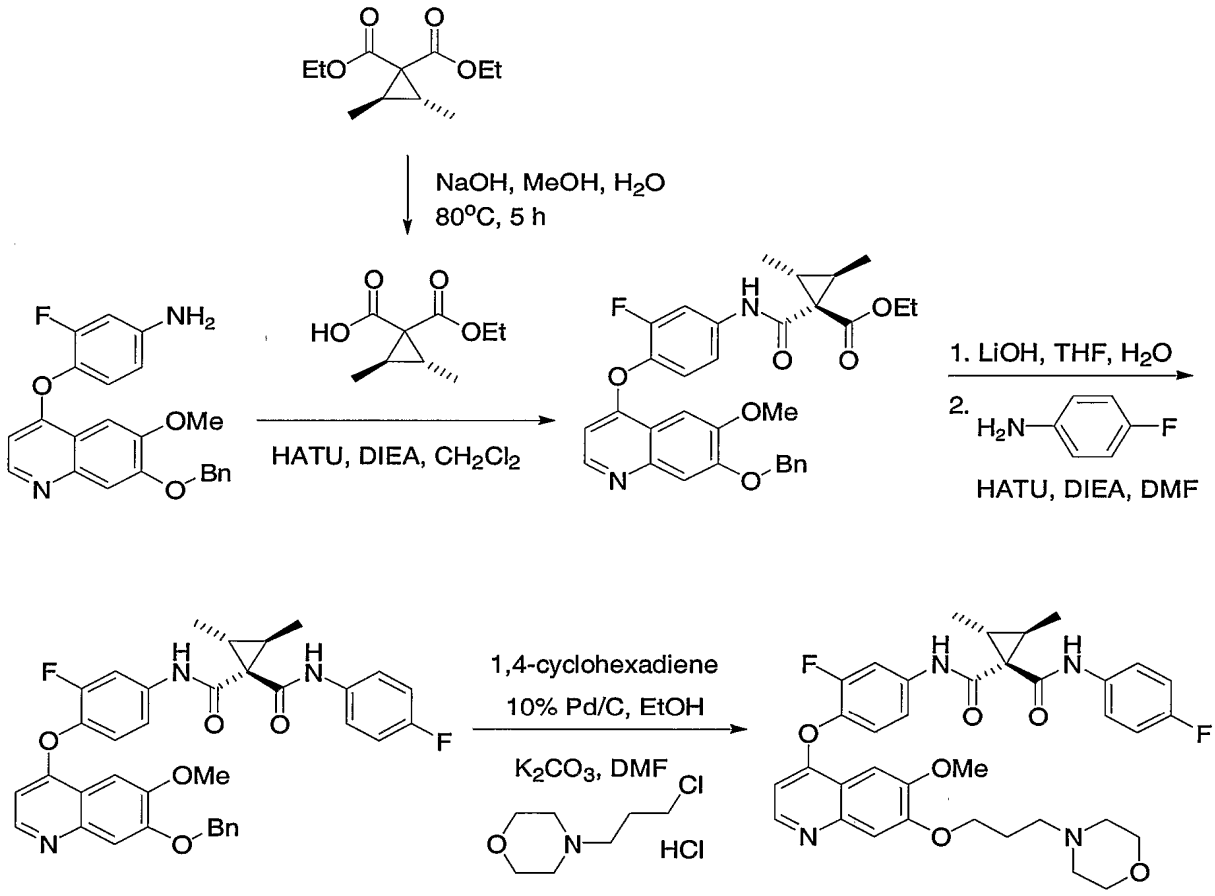
[0438] The crude carboxylic acid (118 mg, 0.23 mmol) and 4-fluoroaniline (111 mg, 0.27 mmol) were dissolved in DMF (2 mL). To this solution was added DIEA (178 mg, 1.38 mmol) and PyBOP (358 mg, 0.69 mmol). The mixture was stirred overnight at rt. It was then diluted with EtOAc, washed twice with brine. Removal of EtOAc and column chromatography gave the desired product.

[0439] The product (66 mg, 0.11 mmol) obtained above was dissolved in EtOH (2 mL). 1,4-cyclohexadiene (80 mg, 1.1 mmol) and 10% Pd/C (10 mg) were added. The mixture was stirred for 2 h under reflux. After cooling, the mixture was filtered through Celite, and washed with MeOH. Removal of the solvents gave the crude product (70 mg), which was used in the next reaction.

[0440] To a solution of the 7-hydroxyquinoline (80 mg, 0.15 mmol) in DMF (2 mL) was added 4-(3-chloropropyl)morpholine hydrochloride (62 mg, 0.31 mmol) and K_2CO_3 (64 mg, 0.46 mmol). The reaction mixture was then stirred at 80 °C for 5 h. After cooling, EtOAc (20 mL) was added. The EtOAc solution was washed twice with brine, and dried over Na_2SO_4. Removal of EtOAc and purification by column chromatography (CH_2Cl_2 : MeOH = 10:1) gave '(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide. The product was then dissolved in ethyl ether, and treated with 1.5 equiv. of 1 N HCl/ether. Filtration and lyophilization gave the HCl salt of '(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-

fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.65 (br s, 1 H), 10.54 (br s, 1 H), 9.74 (s, 1 H), 8.75 (br s, 1 H), 8.01 (br d, J = 12.9 Hz, 1 H), 7.80-7.50 (m, 6 H), 7.20-7.10 (m, 2 H), 6.84 (br s, 1 H), 4.34 (br t, J = 5 Hz, 2 H), 4.04 (s, 3 H), 4.05-3.95 (m, 2 H), 3.77 (br t, J = 11 Hz, 2 H), 3.52 (br d, J = 12.7 Hz, 4 H), 3.12 (br q, J = 9.0 Hz, 2 H), 2.40-2.30 (m, 2 H), 2.10-1.95 (m, 1 H), 1.40-1.30 (m, 2 H), 1.10 (d, J = 6.2 Hz, 3 H).

Example 83



[0441] Synthesis of '(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxyl-quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide. 2,3-trans-Dimethyl-cyclopropane-1,1-dicarboxylic acid diethyl ester was prepared by following the literature procedure. (Ohishi, J. Synthesis, 1980, 690.) To a solution of 2,3-trans-dimethyl-cyclopropane-1,1-dicarboxylic acid diethyl ester (6.75 g, 31.5 mmol) in MeOH (30 mL) was added 33 mL of 1 N NaOH aqueous solution. The mixture was stirred at 85 °C for 5 h. MeOH was removed under reduced pressure; the residue was diluted with 40 mL of H_2O. The aqueous solution was washed with 20 mL of

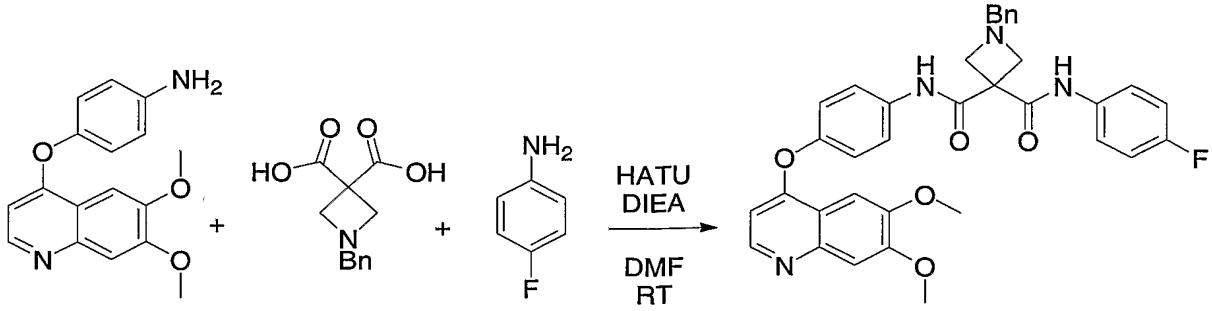
ether, and acidified with 1 N HCl. Filtration and drying under vacuum gave 4.72 g 80 %) of the desired carboxylic acid.

[0442] The aniline (1.08 g, 2.78 mmol) and the carboxylic acid (518 mg, 2.78 mmol) prepared above were dissolved in CH_2Cl_2 (15 mL). HATU (2.11 g, 5.56 mmol) and DIEA (1.8 mL, 11.1 mmol) were added. The reaction mixture was stirred at rt overnight. It was then concentrated and diluted with EtOAc. The EtOAc solution was then washed with 5% NaOH and brine. Removal of EtOAc gave the crude coupling product, which was hydrolyzed to the corresponding carboxylic acid by treatment with $LiOH•H_2O$ (175 mg, 4.17 mmol) in THF (100 mL) -H_2O (50 mL) at 60 °C for 10 h.

[0443] The carboxylic acid (850 mg, 1.60 mmol) and 4-fluoroaniline (355 mg, 3.20 mmol) were dissolved in DMF (8 mL). HATU (3.89 g, 3.2 mmol) and DIEA (1.1 ml, 6.4 mmol) were added. The reaction mixture was stirred at rt overnight. H_2O (10 mL) was added to the reaction, and a precipitate formed. The solid was filtered, washed with aqueous sat. Na_2CO_3 and ether. Further purification by column chromatography gave 596 mg (60%) of the desired product. Debenzylation was done by following the standard procedure.

[0444] To a solution of the 7-hydroxyquinoline (261 mg, 0.49 mmol) in DMF (5 mL) was added 4-(3-chloropropyl)morpholine hydrochloride (195 mg, 0.98 mmol) and K_2CO_3 (202 mg, 1.46 mmol). The reaction mixture was then stirred at 80 °C for 4 h. After cooling, EtOAc (20 mL) was added. The EtOAc solution was washed twice with brine, and dried over Na_2SO_4. Removal of EtOAc and purification by column chromatography (CH_2Cl_2 : MeOH = 10:1) gave 122 mg (37%) of '(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethyl-cyclopropane-1,1-dicarboxamide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 5.1 Hz, 1 H), 8.11 (br s, 1 H), 7.77-7.70 (m, 2 H), 7.53 (s, 1 H), 7.50-7.44 (m, 2 H), 7.40 (s, 1 H), 7.22-7.16 (m, 2 H), 7.06-6.98 (m, 2 H), 6.36 (br d, J = 5.1 Hz, 1 H), 4.26 (t, J = 7.0 Hz, 2 H), 4.02 (s, 3 H), 3.72 (t, J = 4.4 Hz, 4 H), 2.57 (t, J = 7.3 Hz, 2 H), 2.50-2.42 (m, 4 H), 2.18-2.10 (m, 2 H), 1.80-1.66 (m, 2 H), 1.30-1.24 (m, 6 H).

Example 84

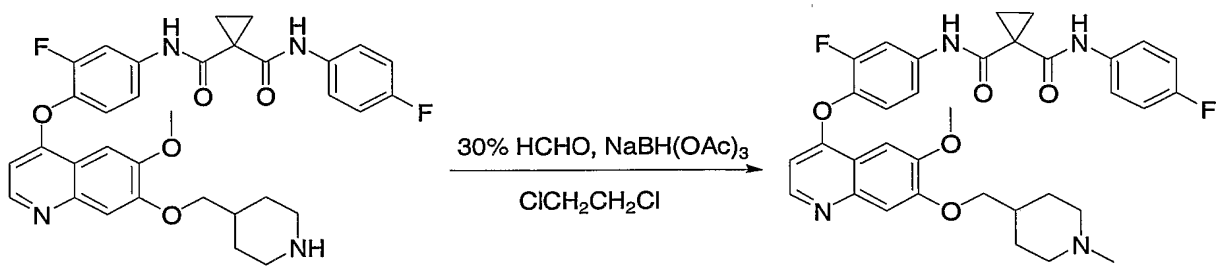


[0445] Synthesis of 'N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide. 1-Benzyl-azetidine-3,3-dicarboxylic acid was prepared by following the literature procedure (Miller, R. A.; et al. Syn. Comm. 2003, 33, 3347). To a solution of 4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylamine (4.2 mmol, 1 equiv.) and 4-fluoroaniline (4.2 mmol, 1 equiv.) in DMF (20 mL) was charged with DIEA (12.6 mmol, 3 equiv.) and a solution of 1-benzyl-azetidine-3,3-dicarboxylic acid (4.2 mmol, 1 equiv.) in DMF (10 mL). The reaction mixture was allowed to stir at RT and monitored by LCMS. The reaction was complete in 6 h. The reaction mixture was diluted with ethyl acetate and washed with 10% LiCl (3x), brine (3x), dried with sodium sulfate, filtered and the solvent was reduced *in vacuo*. The crude product was purified by silica gel chromatography eluting with 2% of MeOH in EtOAc. The fractions containing the desired product were further purified using preparative HPLC to give 'N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide (300 mg, 12% yield) as a white solid. ^{1}HNMR (DMSO-d6): 10.0 (s, 1H), 9.90 (s, 1H), 8.45 (d, 1H), 7.80 (d, 2H), 7.70 (m, 2H), 7.50 (s, 1H), 7.40 (s, 1H), 7.48-7.15 (m, 9H), 3.95 (s, 6H), 3.70 (s, 4H), 3.60 (s, 2H). LCMS (POS): 607.2 (M+H).

[0446] N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) azetidine-3,3-dicarboxamide. To a solution of 'N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide (300 mg, 0.5 mmol) in MeOH (50 mL) was charged with Pd/C (50% wet, 10% mmol, 265 mg) and acetic acid (2 mL). The reaction mixture was subjected to hydrogenolysis condition under H2 (50 psi) on a Parr Hydrogenator for 16 hr. The reaction mixture was filtered through celite and washed with MeOH. After removal of solvent in vacuo, the crude product was purified using preparative HPLC (solvent system: MeCN/H2O/NH4OAc), affording N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)

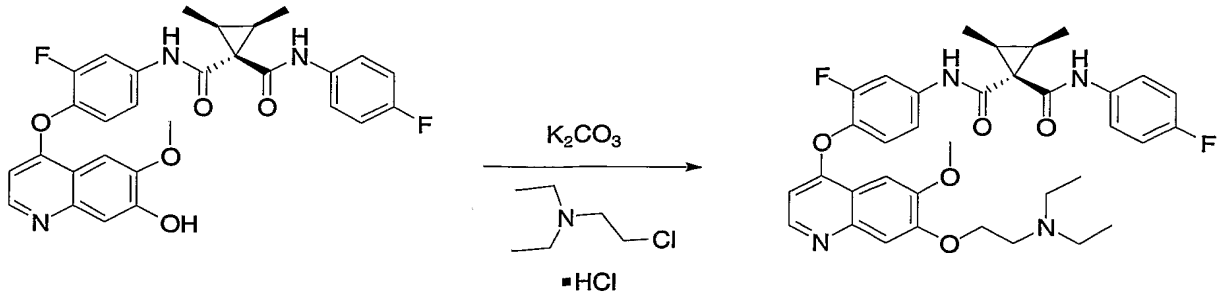
azetidine-3,3-dicarboxamide (82 mg, 32% yield) as a white solid. ^{1}HNMR (DMSO-d6): 8.46 (d, 1H), 7.84 (d, 2H), 7.70 (m, 2H), 7.50 (s, 1H), 7.40 (s, 1H), 7.24 (d, 2H), 7.20 (t, 2H), 6.44 (d, 1H), 4.03 (s, 4H), 3.95 (s, 6H), 1.90 (s, 3H, acetate salt). LCMS (POS): 517.3 (M+H).

Example 85



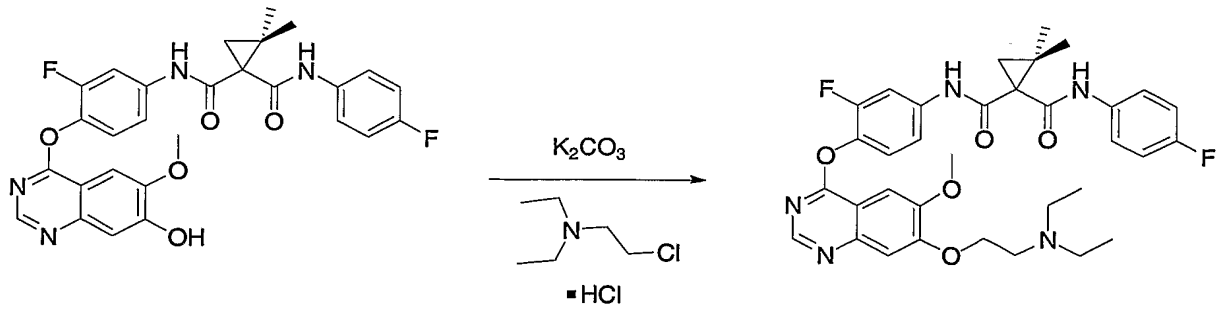
[0447] N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a solution of cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-amide (4-fluoro-phenyl)-amide, TFA salt (~500 mg, 0.71 mmol) in $ClCH_2H_2Cl$ (8 mL) were added 30% formaldehyde (4 mL) and $NaBH(OAc)_3$ (752 mg, 3.55 mmol). The reaction mixture was stirred overnight. It was then quenched with aqueous sat. $NaHCO_3$, extracted with EtOAc. The organic phase was washed with brine and dried over Na_2SO_4. Drying salts were filtered, washed with EtOAc and the filtrate concentrated in vacuo to give 210mgs of crude product. The resulting residue was redissolved in EtOAc and any insoluble material filtered. To the filtrate was added 4M HCl in dioxane (200μl) and the mixture was stirred at room temperature for 1 hour. Solids were filtered, washed with EtOAc, dried under high vacuum, dissolved in 50% aqueous AcCN and lyophilized to give 'N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, HCl salt (113 mg, ~25% yield). ^{1}HNMR (400MHz, DMSO-d6): δ 10.51 (s, 1H), 10.30 (br. s, 1H), 10.04 (s, 1H), 8.80 (d, 1H), 7.99 (dd, 1H), 7.55 (m, 2H), 7.67-7.53 (m, 4H), 7.16 (t, 2H), 6.89 (d, 1H), 4.13 (d, 2H), 4.05 (s, 3H), 3.47 (m, 2H), 3.00 (m, 2H), 2.74 (d, 3H), 2.17 (m, 1H), 2.03 (m, 2H), 1.68 (m, 2H), 1.49 (m, 4H). LC/MS Calcd for $[M+H]^+$ 617.3, found 617.4. Anal. HPLC (8 min gradient): 98% pure, 3.11 min.

Example 86



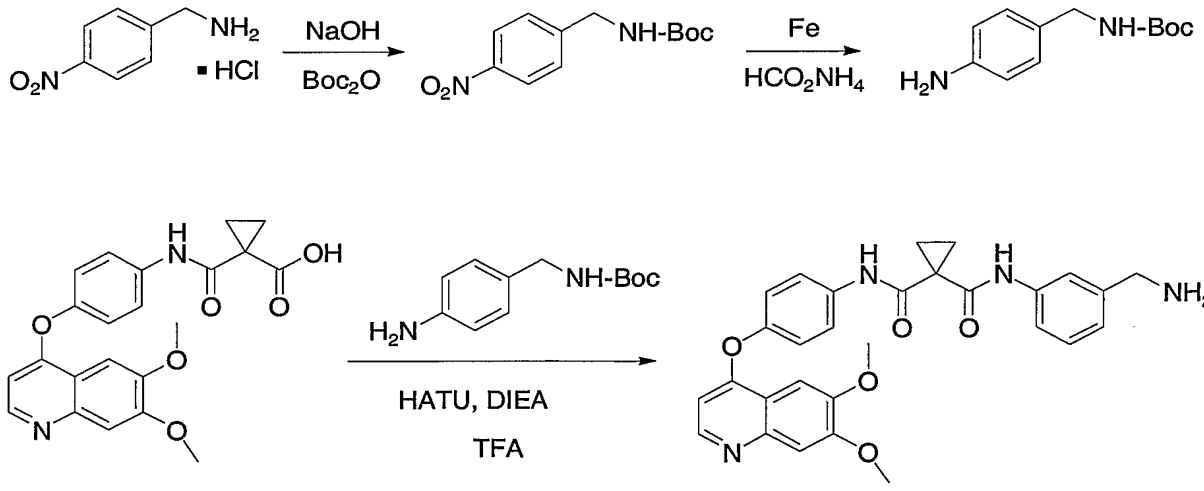
[0448] (1R,2R,3S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide. 2,3-Dimethyl-cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (210 mg, 0.39mmol), DMA (2mls), (2-chloro-ethyl)-diethyl-amine, HCl salt (73 mg, 0.42mmol) and K_2CO_3 (136 mg, 0.98mmol) were combined and heated at 80C overnight. The reaction mixture was then diluted with H_2O and sonicated. The resulting solids were filtered, washed with H_2O and dried under high vacuum. The crude product was then purified by preparative HPLC using an ammonium acetate buffer system and lyophilized to give '(1R,2R,3S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide (39 mg, 16% yield). ^{1}HNMR (400MHz, DMSO-d6): δ 10.14 (s, 1H), 9.61 (s, 1H), 8.46 (d, 1H), 7.87 (dd, 1H), 7.67 (m, 2H), 7.57 (m, 1H), 7.51 (s, 1H), 7.42 (s, 1H), 7.39 (m, 1H), 7.15 (t, 2H), 6.41 (d, 1H), 4.20 (m, 2H), 3.94 (s, 3H), 2.87 (m, 2H), 2.60 (m, 4H), 1.80 (m, 2H), 1.18 (s, 3H), 1.17 (s, 3H), 1.01 (m, 6H). Note: 0.5eq of AcOH is present by NMR. LC/MS Calcd for $[M+H]^+$ 633.3, found 633.4. Anal. HPLC (25 min gradient): 96% pure, 18.52 min.

Example 87



[0449] N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide. 2,2-Dimethyl-cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (203 mg, 0.38mmol), DMA (2mls), (2-chloro-ethyl)-diethyl-amine, HCl salt (73 mg, 0.42mmol) and K_2CO_3 (146 mg, 1.05mmol) were combined and heated at 80C overnight. The reaction mixture was then diluted with H_2O and extracted with CH_2Cl_2 (3x). The combined CH_2Cl_2 extractions were washed with sat'd $NaHCO_3$ (1x), sat'd NaCl (1x), dried (Na_2SO_4), and concentrated in vacuo. The resulting crude product was purified by flash chromatograghy (Silica Gel 60, 100% EtOAc, followed by 10% MeOH, 1% triethylamine in EtOAc), then dissolved in 50% aqueous AcCN and lyophilized to give 'N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethyl-cyclopropane-1,1-dicarboxamide (70 mg, 29% yield). ^{1}HNMR (400MHz, DMSO): δ 10.24 (s, 1H), 10.00 (s, 1H), 8.54 (s, 1H), 7.84 (dd, 1H), 7.66 (m, 2H), 7.56 (s, 1H), 7.51 (m, 1H), 7.43 (m, 2H), 7.18 (t, 2H), 4.26 (m, 2H), 3.98 (s, 3H), 2.88 (m, 2H), 2.59 (m, 4H), 1.58 (m, 2H), 1.18 (s, 6H), 1.00 (t, 6H). LC/MS Calcd for $[M+H]^+$ 634.3, found 634.4. Anal. HPLC (25 min gradient): 94% pure, 24.08 min.

Example 88



[0450] Synthesis of 'N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide. (4-Nitro-benzyl)-carbamic acid tert-butyl ester. 4-Nitro-benzylamine, HCl salt (5.19g, 27.5mmol) was dissolved in dioxane (100mls). NaOH (3.4g, 85.0mmol) in H_2O (20mls) was added, followed by Boc

anhydride (7.6g, 34.8mmol). The mixture was stirred at room temperature. After 3hrs, the reaction mixture was diluted with EtOAc and washed with H_2O (3x), sat'd NaCl (1x), dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was triturated with hexanes, the resulting solids filtered, washed with hexanes and dried under vacuum to give (4-nitro-benzyl)-carbamic acid tert-butyl ester (6.34g, 91% yield). LC/MS Calcd for $[M+H]^+$ 253.1, found 197.0 (minus t-butyl).

[0451] (4-Amino-benzyl)-carbamic acid tert-butyl ester. (4-Nitro-benzyl)-carbamic acid tert-butyl ester (6.34g, 25.1mmol), iron powder (6.5g, 116mmol), ammonium formate (13.0g, 206mmol), H_2O (75mls), and toluene (75mls) were combined and heated to reflux. After 3hrs the reaction mixture was allowed to cool and filtered through Celite with thorough washing with EtOAc. The filtrate was transferred to a separatory funnel and the phases separated. The organic phase was further washed with H_2O (1x), sat'd NaCl (1x), dried (Na_2SO_4), and concentrated in vacuo to give (4-amino-benzyl)-carbamic acid tert-butyl ester (5.02g, 90% yield). LC/MS Calcd for $[M+H]^+$ 223.1, found 167.1 (minus t-butyl).

[0452] [3-({1-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropane-carbonyl}-amino)-benzyl]-carbamic acid tert-butyl ester. 1-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropanecarboxylic acid (254 mg, 0.62mmol), (4-amino-benzyl)-carbamic acid tert-butyl ester (164 mg, 0.74mmol), dry DMA (10mls), HATU (714 mg, 1.88mmol), and DIEA (325ml, 1.86mmol) were combined and stirred at room temperature. After 2hrs, the reaction mixture is diluted with H_2O and the resulting solids are filtered, washed with H_2O, followed by sat'd $NaHCO_3$, and dried under high vacuum to give crude [3-({1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropanecarbonyl}-amino)-benzyl]-carbamic acid tert-butyl ester (301 mg, 79% yield) which was used in the next reaction without further purification. LC/MS Calcd for $[M+H]^+$ 613.3, found 613.1.

[0453] N-[3-(Aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl) cyclopropane-1,1-dicarboxamide, TFA salt. [3-({1-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenylcarbamoyl]-cyclopropanecarbonyl}-amino)-benzyl]-carbamic acid tert-butyl ester (50 mg, 0.081mmol) was dissolved in 50% TFA in CH_2Cl_2 (10mls) and stirred at room temperature. After 2hrs, the reaction mixture was concentrated in vacuo and the resulting residue was triturated with Et_2O. The resulting solids were filtered, washed with Et_2O and dried under high vacuum to give 'N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-

bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide as the TFA salt (54 mg, 100%). ^{1}HNMR (400MHz, DMSO-d6): δ 10.28 (s, 1H), 10.19 (s, 1H), 8.77 (m, 1H), 8.21 (m, 3H), 7.84 (m, 2H), 7.76 (m, 1H), 7.71 (m, 1H), 7.58 (m, 2H), 7.38 (m, 3H), 7.19 (m, 1H), 6.76 (m, 1H), 4.03 (s, 6H), 3.39 (m, 2H), 1.53 (m, 4H). Note: all peaks are very broad and unresolved. LC/MS Calcd for $[M+H]^+$ 513.2, found 513.4. Anal. HPLC (25 min gradient): 88% pure, 12.39 min.

[0454] Table 3 contains ^{1}H-NMR data for selected compounds of the invention.

Table 3

Entry	Name	^{1}H-NMR
1	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.52 (s, 1H), 10.02 (s, 1H), 9.38 (br., 3H), 8.79 (d, 1H), 7.98 (dd, 1H), 7.74 (s, 1H), 7.65 (m, 3H), 7.54 (m, 2H), 7.15 (t, 2H), 6.86 (d, 1H), 4.33 (t, 2H), 4.04 (s, 3H), 3.17-3.50 (m, 9H), 2.27 (br., 2H), 1.79 (m, 1H), 1.48 (m, 4H). Note: The peak at δ9.38 includes 2 TFA equivalents.
2	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.41 (s, 1H), 10.03 (s, 1H), 8.47 (d, 1H), 7.90 (dd, 1H), 7.64 (m, 2H), 7.52 (s, 2H), 7.42 (t, 1H), 7.39 (s, 1H), 7.16 (t, 2H), 6.41 (d, 1H), 4.18 (t, 2H), 3.95 (s, 3H), 2.47 (t, 2H), 2.6-2.8 (br., 8H), 2.17 (s, 3H), 1.97 (m, 2H), 1.48 (s, 4H).
3	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	1H NMR (400MHz, DMSO-d6): d 10.51 (s, 1H), 10.30 (br. s, 1H), 10.04 (s, 1H), 8.80 (d, 1H), 7.99 (dd, 1H), 7.55 (m, 2H), 7.67-7.53 (m, 4H), 7.16 (t, 2H), 6.89 (d, 1H), 4.13 (d, 2H), 4.05 (s, 3H), 3.47 (m, 2H), 3.00 (m, 2H), 2.74 (d, 3H), 2.17 (m, 1H), 2.03 (m, 2H), 1.68 (m, 2H), 1.49 (m, 4H).
4	N-(4-fluorophenyl)-N'-[4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d6): 8.47 (d, 1H), 8.30 (m, 1H), 8.15 (m, 1H), 7.8 (m, 2H), 7.62 (s, 1H), 7.45 (m, 2H), 7.2 (m, 3H), 7.10 (m, 2H), 6.7 (d, 1H), 4.5 (m, 2H), 4.3 (m, 2H), 4.01(s, 3H), 3.5 (br, 2H), 3.3 (m, 2H), 3.1 (m, 2H), 2.51 (m, 2H), 1.9 (m, 2H) 1.6 (m, 4H).
5	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d6): 10.58 (s, 1H), 10.31 (bs, 1H), 10.04 (s, 1H), 8.75 (d, 1H), 7.99 (d, 1H), 7.74 (s, 1H), 7.63 (m, 4H), 7.19 (t, 2H), 6.91 (m, 1H), 4.39 (t, 2H), 4.19 (s, 3H), 3.21 (m, 7H), 2.29 (m, 2H), 1.46 (d, 4H), 1.15 (t, 6H).

Table 3

Entry	Name	^{1}H-NMR
6	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 11.56 (s, 1H), 9.77 (s, 1H), 8.50 (d, 1H), 8.32 (d, 1H), 7.82 (d, 1H), 7.59 (m, 2H), 7.51 (s, 1H), 7.42 (s, 1H), 7.20 (t, 2H), 6.55 (d, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 1.73 (m, 2H), 3.65 (m, 2H).
7	N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.34 (s, 1H), 9.94 (s, 1H), 7.83 (d, 1H), 7.59 (m, 2H), 7.56 (m, 1H), 7.40 (m, 2H), 7.23 (s, 1H), 7.09 (t, 2H), 6.12 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.48 (s, 3H), 1.40 (m, 4H).
8	N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) 10.15 (bs, 1H), 10.01 (bs, 1H), 7.69-7.75 (m, 2H), 7.61-7.68 (m, 2H), 7.52 (s, 1H), 7.32 (s, 1H), 7.23-7.29 (m, 2H), 7.12-7.19 (m, 2H), 3.93 (d, 6H), 2.43 (s, 3H), 1.53 (s, 4H).
9	N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6) d 10.34 (s, 1H), 9.95 (s, 1H), 7.82 (d, 1H), 7.58 (m, 2H), 7.44 (d, 1H), 7.33 (t, 1H), 7.25 (s, 1H), 7.09 (t, 2H), 7.07 (s, 1H), 6.17 (br s, 2H), 5.66 (s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 1.40 (d, 4H).
10	N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.42 (s, 1H), 9.91 (s, 1H), 7.88 (dd, 1H), 7.56 (m, 2H), 7.44 (m, 4H), 7.09 (t, 2H), 5.90 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.39 (br s, 1H), 2.92 (s, 3H), 1.41 (dt, 4H).
11	(1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6) d 10.49 (br s, 1 H), 10.26 (br s, 1 H), 10.15 (br s, 1 H), 8.74 (br s, 1 H), 7.95 (br d, J = 13.2 Hz, 1 H), 7.8-7.5 (m, 6 H), 7.16 (t, J = 8.9 Hz, 2 H), 6.82 (br s, 1 H), 4.34 (t, J = 5.9 Hz, 2 H), 4.02 (s, 3 H), 3.99 (br s, 2 H), 3.77 (br t, J = 12.0 Hz, 2 H), 3.56-3.30 (m, 4 H), 3.17-3.07 (m, 2 H), 2.40-2.30 (m, 2 H), 2.04-1.95 (m, 1 H), 1.45 (dd, J = 7.2, 4.7 Hz, 1 H), 1.36 (dd, J = 8.5, 4.5 Hz, 1 H), 1.09 (d, J = 6.2 Hz, 3 H).

Table 3

Entry	Name	^{1}H-NMR
12	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6) d 10.65 (br s, 1 H), 10.54 (br s, 1 H), 9.74 (s, 1 H), 8.75 (br s, 1 H), 8.01 (br d, J = 12.9 Hz, 1 H), 7.80-7.50 (m, 6 H), 7.20-7.10 (m, 2 H), 6.84 (br s, 1 H), 4.34 (br t, J = 5 Hz, 2 H), 4.04 (s, 3 H), 4.05-3.95 (m, 2 H), 3.77 (br t, J = 11 Hz, 2 H), 3.52 (br d, J = 12.7 Hz, 4 H), 3.12 (br q, J = 9.0 Hz, 2 H), 2.40-2.30 (m, 2 H), 2.10-1.95 (m, 1 H), 1.40-1.30 (m, 2 H), 1.10 (d, J = 6.2 Hz, 3 H).
13	N-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.37 (br s, 1H), 10.00 (s, 1H), 8.44 (d, 1H), 7.87 (d, 1H), 7.62 (m, 2H), 7.49 (m, 2H), 7.41 (m, 2H), 7.13 (t, 2H), 6.40 (d, 1H), 4.17 (t, 2H), 3.93 (s, 3H), 2.59 (t, 2H), 2.49 (m, 6H), 1.91 (m, 4H), 0.94 (t, 6H).
14	N-(4-{[6-{[2-(diethylamino)ethyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.36 (br s, 1H), 9.99 (s, 1H), 8.44 (d, 1H), 7.88 (dd, 1H), 7.62 (m, 2H), 7.57 (m, 2H), 7.41 (m, 2H), 7.13 (t, 2H), 6.40 (d, 1H), 4.17 (t, 2H), 3.93 (s, 3H), 2.85 (t, 2H), 2.56 (q, 4H), 2.49 (m, 4H), 0.98 (t, 6H).
15	1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[(1-{[(4-fluorophenyl)amino]carbonyl}cyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate	^{1}H NMR (400 MHz, $CDCl_3$): 10.05 (s, 1H), 8.49-8.27 (t, 1H), 7.79-7.76 (d, 1H), 7.57 (s, 1H), 7.47-7.43 (m, 3H), 7.27-7.20 (m, 1H), 7.09-7.04 (m, 2H), 6.40-6.39 (d, 1H), 4.28-4.25 (t, 2H), 3.50 (s, 3H), 3.47-3.44, (t, 4H), 2.62-2.59 (t, 2H), 2.46-2.44 (t, 4H), 2.18-2.11 (m, 2H), 2.09 (s, 1H), 1.83-1.81 (t, 2H), 1.64-1.61 (t, 2H), 1.47 (s, 9H).
16	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.40 (s, 1H), 9.65 (s, 1H), 8.45 (s, 1H), 7.79 (dd, 1H), 7.53 (m, 2H), 7.47 (s, 1H), 7.36 (m, 1H), 7.31 (m, 2H), 7.05 (t, 2H), 4.17 (t, 2H), 3.91 (s, 3H), 3.51 (t, 4H), 2.40 (t, 2H), 2.36 (m, 4H), 1.90 (m, 3H), 1.30 (m, 2H), 1.02 (d, 3H).
17	(1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.49 (s, 1H), 9.73 (s, 1H), 8.52 (s, 1H), 7.85 (dd, 1H), 7.61 (m, 2H), 7.54 (s, 1H), 7.41 (m, 3H), 7.12 (t, 2H), 7.23 (t, 2H), 3.96 (s, 3H), 2.86 (t, 2H), 2.56 (q, 4H), 1.98 (m, 1H), 1.34 (m, 2H), 1.07 (d, 3H), 0.97 (t, 6H).

Table 3

Entry	Name	^{1}H-NMR
18	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6) 8.51 (s, 1H), 7.78-7.84 (m, 1H), 7.58-7.64 (m, 2H), 7.53 (s, 1H), 7.34-7.48 (m, 3H), 7.13 (t, 2H), 4.22 (t, 2H), 3.98 (s, 3H), 2.84 (t, 2H), 2.55 (q, 4H), 1.48 (s, 4H), 1.39 (t, 6H).
19	N-(4-{[7-{[3-(4-acetylpiperazin-1-yl)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, $CDCl_3$): 10.04 (s, 1H), 8.48-8.47 (d, 1H), 8.21 (s, 1H), 7.79-7.76 (d, 1H), 7.57 (s, 1H), 7.52-7.44 (m, 3H), 7.28-7.20 (m, 2H), 7.09-7.05 (t, 2H), 6.40-6.39 (d, 1H), 4.30-4.26 (t, 2H), 4.04 (s, 3H), 3.64-3.62 (t, 2H), 3.49-3.47 (t, 2H), 2.62-2.58 (t, 2H), 2.50-2.44 (m, 4H), 2.17-2.12 (m, 2H), 2.10 (s, 3H), 1.84-1.81 (t, 2H), 1.64-1.61 (t, 2H).
20	1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[((1R,2R)-1-{[(4-fluorophenyl)amino]carbonyl}-2-methylcyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate	^{1}H NMR (400 MHz, DMSO-d_6): 10.54 (s, 1H), 9.72 (s, 1H), 8.47-8.46 (d, 1H), 7.96-7.93 (dd, 1H), 7.63-7.61 (m, 2H), 7.52 (br s, 2H), 7.42-7.40 (d, 2H), 7.17-7.12 (t, 2H), 6.44-6.42 (d, 1H), 4.22-4.18 (t, 2H), 3.95 (s, 3H), 3.42-3.40 (m, 2H), 2.36-2.26 (m, 8H), 2.00-1.98 (m, 3H), 1.58-1.54 (m, 2H), 1.40 (s, 9H), 1.10-1.09 (d, 3H).
21	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide	1H NMR (DMSO-d6): 10.0 (s, 1H), 9.9 (s, 1H), 8.45 (d, 1H), 7.8 (d, 2H), 7.7 (m, 2H), 7.5 (s, 1H), 7.4 (s, 1H), 7.48-7.15 (m, 9H), 3.95 (s, 6H), 3.7 (s, 4H), 3.6 (s, 2H).
22	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)azetidine-3,3-dicarboxamide	1H NMR (DMSO-d6): 8.46 (d, 1H), 7.84 (d, 2H), 7.70 (m, 2H), 7.50 (s, 1H), 7.40 (s, 1H), 7.24 (d, 2H), 7.20 (t, 2H), 6.44 (d, 1H), 4.03 (s, 4H), 3.95 (s, 6H), 1.90 (s, 3H, acetate salt).
23	(1R,2S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6): 10.26 (s, 1H), 9.75 (s, 1H), 8.47-8.46 (d, 1H), 7.91-7.87 (dd, 1H), 7.70-7.66 (m, 2H), 7.56-7.51 (m, 2H), 7.43-7.38 (m, 2H), 6.42-6.41 (d, 1H), 4.20-4.16 (t, 2H), 3.95 (s, 3H), 2.47-2.43 (m, 2H), 2.40-2.24 (m, 5H), 2.14 (s, 3H), 2.03-1.93 (m, 3H), 1.89 (s, 3H), 1.45-1.42 (m, 1H), 1.38-1.35 (m, 1H), 1.10-1.08 (d, 3H).

Table 3

Entry	Name	^{1}H-NMR
24	(1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6): 10.56 (s, 1H), 9.75 (s, 1H), 8.47-8.46 (d, 1H), 7.96-7.93 (d, 1H), 7.68-7.61 (m, 2H), 7.53-7.52 (m, 2H), 7.44-7.39 (m, 2H), 7.18-7.12 (m, 2H), 6.44-6.42 (d, 1H), 4.20-4.17 (t, 2H), 3.95 (s, 3H), 3.42-3.30 (m, 3H), 2.46-2.44 (m, 2H), 2.33 (br s, 2H), 2.15 (s, 3H), 2.05-1.94 (m, 2H), 1.89 (s, 5H), 1.40-1.35 (m, 1H), 1.10-1.09 (m, 3H).
25	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6): 10.55 (s, 1H), 9.72 (s, 1H), 8.47-8.46 (d, 1H), 7.96-7.93 (d, 1H), 7.68-7.61 (m, 2H), 7.52 (br s, 2H), 7.44-7.40 (m, 2H), 7.17-7.12 (m, 2H), 6.44-6.43 (d, 1H), 4.21-4.18 (t, 2H), 3.95 (s, 3H), 2.79 (br s, 4H), 2.47-2.44 (t, 2H), 2.38 (br s, 3H), 2.04-1.95 (m, 3H), 1.40-1.35 (m, 2H), 1.11-1.09 (m, 5H).
26	N-(3-fluoro-4-{[7-({3-[4-(1-methylethyl)piperazin-1-yl]propyl}oxy)-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6): 10.40 (s, 1H), 10.02 (s, 1H), 8.47-8.46 (d, 1H), 7.92-7.89 (d, 1H), 7.66-7.63 (m, 2H), 7.52-7.51 (d, 2H), 7.44-7.39 (m, 2H), 7.19-7.14 (m, 2H), 6.42-6.41 (d, 1H), 4.20-4.17 (t, 2H), 3.95 (s, 3H), 2.70-2.68 (m, 1H), 2.62-2.55 (m, 2H), 2.46-2.33 (m, 8H), 1.99-1.94 (m, 2H), 1.47 (s, 4H), 1.00-0.95 (m, 6H).
27	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6)10.34 (s, 1H), 10.01 (s, 1H), 8.50 (s, 1H), 7.81 (dd, 1H), 7.55-7.68 (m, 2H), 7.51-7.55 (m, 2H), 7.33-7.48 (m, 3H), 7.12 (t, 2H), 4.22 (t, 2H), 3.94 (s, 3H), 2.52-2.61 (m, 2H), 2.49-2.51 (m, 4H), 1.83-1.94 (m, 2H), 1.42 (s, 4H), 0.95 (t, 6H).
28	(1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.52 (s, 1H), 9.70 (s, 1H), 8.44 (d, 1H), 7.92 (dd, 1H), 7.61 (m, 2H), 7.50 (m, 2H), 7.43 (m, 2H), 7.12 (t, 2H), 6.41 (d, 1H), 4.17 (t, 2H), 3.93 (s, 3H), 2.55 (m, 2H), 2.31 (m, 4H), 1.98 (m, 1H), 1.88 (m, 2H), 1.35 (m, 2H), 1.07 (d, 3H), 0.94 (t, 6H).
29	(1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.52 (s, 1H), 9.70 (s, 1H), 8.44 (d, 1H), 7.78 (dd, 1H), 7.61 (m, 2H), 7.51 (m, 2H), 7.41 (m, 2H), 7.12 (t, 2H), 6.41 (d, 1H), 4.17 (t, 2H), 3.93 (s, 3H), 2.85 (t, 2H), 2.57 (q, 4H), 1.98 (m, 1H), 1.34 (m, 2H), 1.07 (d, 3H), 0.98 (t, 6H).

Table 3

Entry	Name	^{1}H-NMR
30	(1R,2S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.17 (s, 1H), 9.97 (s, 1H), 8.39 (d, 1H), 7.80 (dd, 1H), 7.62 (m, 2H), 7.45 (m, 2H), 7.31 (m, 2H), 7.09 (t, 2H), 6.34 (d, 1H), 4.12 (t, 2H), 3.88 (s, 3H), 2.46 (m, 2H), 2.40 (m, 4H), 1.92 (m, 1H), 1.84 (m, 2H), 1.37 (m, 1H), 1.29 (m, 1H), 1.01 (d, 3H), 0.89 (t, 6H).
31	(1R,2S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (DMSO-d_6) d 10.22 (s, 1H), 10.01 (s, 1H), 8.44 (d, 1H), 7.86 (dd, 1H), 7.66 (m, 2H), 7.49 (m, 2H), 7.39 (m, 2H), 7.14 (m, 2H), 6.39 (d, 1H), 4.18 (m, 2H), 3.92 (s, 3H), 2.85 (t, 2H), 2.57 (q, 4H), 1.97 (m, 1H), 1.42 (m, 1H), 1.35 (m, 1H), 1.06 (d, 3H), 0.98 (t, 6H).
32	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	^{1}H NMR ($CDCl_3$) 8.57 (s, 1H), 8.12 (s, 1H), 7.73-7.81 (m, 2H), 7.48-7.53 (m, 2H), 7.32 (s, 1H), 6.98-7.08 (m, 3H), 4.28 (t, 2H), 4.04 (s, 3H), 3.25 (t, 2H), 2.76 (q, 4H), 2.67 (q, 4H), 2.01-2.15 (m, 2H), 1.10 (t, 6H).
33	(1R,2S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6): 10.28 (s, 1H), 9.80 (s, 1H) 8.47-8.46 (d, 1H), 7.90-7.88 (d, 1H), 7.70-7.62 (m, 2H), 7.56-7.52 (m, 2H), 7.44-7.39 (m, 2H), 7.18-7.12 (m, 2H), 6.44-6.41 (t, 1H), 4.20-4.17 (t, 2H), 3.95 (s, 3H), 2.74-2.72 (t, 3H), 2.46-2.42 (m, 1H), 2.35 (br s, 3H), 2.03-1.93 (m, 3H), 1.87 (s, 4H), 1.43-1.35 (m, 2H), 1.09-1.08 (m, 3H).
34	(1r,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 1H (10.12 ppm, s), 1H (9.6 ppm, s), 1H (8.46 ppm, d), 1H (7.88 ppm, dd), 2H (7.68 ppm, m), 1H (7.56 ppm, d), 1H (7.51 ppm, s), 2H(7.4 ppm, m), 2H (7.13 ppm, t), 1H (6.4 ppm, d), 2H (4.2 ppm, t), 3H (3.94 ppm, s), 4H (3.6 ppm, t), 2H (2.45 ppm, t), 4H (2.37 ppm, m), 2H (1.97 ppm, t), 2H (1.8 ppm, m), 6 H(1.28 ppm, d).
35	(1r,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 1H (10.12 ppm, s), 1H (9.6 ppm, s), 1H (8.46 ppm, d), 1H (7.88 ppm, dd), 2H (7.69 ppm, m), 1H (7.58 ppm, d), 1H (7.51 ppm, s), 2H (7.4 ppm, m), 2H (7.13 ppm, t), 1H (6.4 ppm, d), 2H (4.2 ppm, t), 3H (3.95 ppm, s), 10H (2.35 ppm, m), 3H (2.14 ppm, s), 2H (1.97 ppm, t), 2H (1.8 ppm, m), 6H (1.28 ppm, d).

Table 3

Entry	Name	^{1}H-NMR
36	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d6): 8.45 (d, 2 H), 8.15 (d, 1H), 7.8 (d, 1H), 7.45 (m, 3H), 7.25 (m, 3H), 7.0 (m, 2H), 4.20 (t, 2H), 4.0 (s, 3H), 3.7 (m, 4H), 2.67 (m, 4H), 2.45 (m, 6H), 2.0 (m, 4H).
37	(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, $CDCl_3$) d 8.44 (d, J = 5.1 Hz, 1 H), 8.11 (br s, 1 H), 7.77-7.70 (m, 2 H), 7.53 (s, 1 H), 7.50-7.44 (m, 2 H), 7.40 (s, 1 H), 7.22-7.16 (m, 2 H), 7.06-6.98 (m, 2 H), 6.36 (br d, J = 5.1 Hz, 1 H), 4.26 (t, J = 7.0 Hz, 2 H), 4.02 (s, 3 H), 3.72 (t, J = 4.4 Hz, 4 H), 2.57 (t, J = 7.3 Hz, 2 H), 2.50-2.42 (m, 4 H), 2.18-2.10 (m, 2 H), 1.80-1.66 (m, 2 H), 1.30-1.24 (m, 6 H).
38	(2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6) d 10.34 (s, 1 H), 10.05 (s, 1 H), 8.46 (br s, 1 H), 7.93 (br d, J = 4.7 Hz, 1 H), 7.54-7.52 (m, 2 H), 7.52-7.50 (m, 2 H), 7.50-7.30 (m, 2 H), 7.20-7.10 (m, 2 H), 6.47 (br s, 1 H), 4.30-4.20 (m, 2 H), 3.95 (s, 3 H), 3.40-3.10 (m, 6 H), 2.60-2.40 (m, 2 H), 1.90-1.80 (m, 2 H), 1.30-1.10 (m, 12 H).
39	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	1H NMR (400MHz, DMSO-d6): d 10.47 (s, 1H), 10.16 (s, 1H), 8.43 (d, 1H), 7.92 (dd, 1H), 7.67 (m, 2H), 7.58 (m, 1H), 7.52 (s, 1H), 7.41 (m, 2H), 7.15 (t, 2H), 6.44 (d, 1H), 4.25 (t, 2H), 3.95 (s, 3H), 3.10 (m, 6H), 2.17 (m, 2H), 1.91 (s, 3H, acetate salt), 1.52 (m, 2H), 1.18 (m, 12H).
40	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	1H NMR (400MHz, DMSO-d6): d 10.21 (s, 1H), 9.97 (s, 1H), 8.51 (s, 1H), 7.81 (dd, 1H), 7.64 (m, 2H), 7.54 (s, 1H), 7.48 (m, 1H), 7.41 (m, 1H), 7.38 (s, 1H), 7.15 (t, 2H), 4.24 (t, 2H), 3.97 (s, 3H), 3.58 (m, 4H), 2.45 (t, 2H), 2.38 (m, 4H), 1.97 (m, 2H), 1.58 (m, 2H), 1.18 (s, 3H), 1.17 (s, 3H).
41	(1R,2R,3S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	1H NMR (400MHz, DMSO-d6): d 10.14 (s, 1H), 9.61 (s, 1H), 8.46 (d, 1H), 7.87 (dd, 1H), 7.67 (m, 2H), 7.57 (m, 1H), 7.51 (s, 1H), 7.42 (s, 1H), 7.39 (m, 1H), 7.15 (t, 2H), 6.41 (d, 1H), 4.20 (m, 2H), 3.94 (s, 3H), 2.87 (m, 2H), 2.60 (m, 4H), 1.80 (m, 2H), 1.18 (s, 3H), 1.17 (s, 3H), 1.01 (m, 6H). Note: 0.5eq of AcOH is present by NMR.

Table 3

Entry	Name	^{1}H-NMR
42	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	1H NMR (400MHz, DMSO): d 10.24 (s, 1H), 10.00 (s, 1H), 8.54 (s, 1H), 7.84 (dd, 1H), 7.66 (m, 2H), 7.56 (s, 1H), 7.51 (m, 1H), 7.43 (m, 2H), 7.18 (t, 2H), 4.26 (m, 2H), 3.98 (s, 3H), 2.88 (m, 2H), 2.59 (m, 4H), 1.58 (m, 2H), 1.18 (s, 6H), 1.00 (t, 6H).
43	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	1H NMR (400MHz, DMSO-d6): d 10.21 (s, 1H), 9.97 (s, 1H), 8.51 (s, 1H), 7.82 (dd, 1H), 7.64 (m, 2H), 7.54 (s, 1H), 7.48 (m, 1H), 7.41 (m, 1H), 7.37 (s, 1H), 7.15 (t, 2H), 4.23 (t, 2H), 3.97 (s, 3H), 2.56 (m, 2H), 2.46 (m, 4H), 1.91 (m, 2H), 1.58 (m, 2H), 1.18 (s, 6H), 0.96 (t, 6H).
44	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	1H NMR (CDCl3): 8.57 (s, 1H), 8.50 (s, 1H), 8.11 (s, 1H), 7.81 (dd, 1H), 7.53 (m, 3H), 7.28 (m, 4H), 7.04 (t, 2H), 4.24 (t, 2H), 4.04 (s, 3H), 2.95 (t, 2H), 2.84 (q, 4H), 2.75 (m, 4H), 2.21 (m, 2H), 2.02 (m, 2H), 1.18 (t, 6H).
45	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	1H NMR (CDCL3): 8.57 (s, 1H), 8.49 (s, 1H), 8.10 (s, 1H), 7.80 (d, 1H), 7.70 (br., 1H), 7.52 (m, 3H), 7.31 (m, 3H), 7.04 (t, 2H), 4.26 (t, 2H), 4.04 (s, 3H), 2.62-2.77 (m, 14H), 2.40 (s, 3H), 2.13 (m, 2H), 2.01 (m, 2H).
46	(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, $CDCl_3$) d 8.59 (s, 1 H), 8.11 (br s, 1 H), 7.80-7.76 (m, 2 H), 7.53 (s, 1 H), 7.50-7.46 (m, 2 H), 7.34 (s, 1 H), 7.26-7.24 (m, 2 H), 7.06-7.00 (m, 2 H), 4.28 (t, J = 6.6 Hz, 2 H), 4.05 (s, 3 H), 3.73 (br t, J = 4.4 Hz, 4 H), 2.57 (t, J = 7.0 Hz, 2 H), 2,52-2,45 (m, 4 H), 2.18-2.10 (m, 2 H), 1.80-1.68 (m, 2 H), 1.28-1.20 (m, 6 H).
47	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6): 9.98 (s, 1H), 9.72 (s, 1H), 8.45-8.43 (d, 1H), 7.97-7.94 (dd, 1H), 7.73-7.69 (m, 2H), 7.65-7.52 (m, 3H), 7.44-7.39 (m, 1H), 7.18-7.14 (m, 2H), 6.43-6.42 (d, 1H), 4.20-4.19 (t, 2H), 3.95 (s, 3H), 2.70-2.66 (m, 6H), 2.45 (br s, 2H), 1.91-1.84 (m, 6H), 0.98 (br s, 6H).

Table 3

Entry	Name	^{1}H-NMR
48	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	^{1}H NMR (400 MHz, DMSO-d_6): 9.99 (s, 1H), 9.73 (s, 1H), 8.45-8.43 (d, 1H), 7.97-7.93 (dd, 1H), 7.73-7.69 (m, 2H), 7.65-7.52 (m, 2H), 7.44-7.38 (m, 2H), 7.18-7.14 (m, 2H), 6.43-6.42 (d, 1H), 4.19-4.16 (t, 3H), 3.95 (s, 3H), 2.70-2.66 (m, 4H), 2.47-2.33 (m, 8H), 2.15 (s, 3H), 1.98-1.94 (m, 2H), 1.90-1.84 (m, 4H).
49	(2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, $CDCl_3$) d 8.59 (br s, 1 H), 8.29 (br s, 1 H), 7.93 (s, 1 H), 7.77 (d, J = 10.8 Hz, 1 H), 7.53 (s, 1 H), 7.50-7.45 (m, 2 H), 7.32 (s, 1 H), 7.26-7.22 (m, 2 H), 7.05-6.99 (m, 2 H), 4.27 (t, J = 6.6 Hz, 2 H), 4.04 (s, 3 H), 3.03 (t, J = 6.5 Hz, 2 H), 2.67 (q, J = 7.0 Hz, 4 H), 1.80-1.70 (m, 2 H), 1.22 (br t, J = 5.3 Hz, 6 H), 1.09 (br t, J = 7.2 Hz, 6 H).
50	(2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, $CDCl_3$) d 8.58 (s, 1 H), 8.40-8.36 (m, 1 H), 8.02-7.96 (m, 1 H), 7.80-7.75 (m, 1 H), 7.53 (s, 1 H), 7.52-7.50 (m, 2 H), 7.31 (s, 1 H), 7.28-7.20 (m, 2 H), 7.02 (t, J = 8.5 Hz, 2 H), 4.25 (t, J = 6.3 Hz, 2 H), 4.04 (s, 3 H), 3.00-2.90 (m, 2 H), 2.88-2.80 (m, 4 H), 2.30-2.20 (m, 2 H), 1.76-1.68 (m, 2 H), 1.25-1.15 (m, 12 H).
51	(2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	^{1}H NMR (400 MHz, $CDCl_3$) d 8.47 (d, J = 5.2 Hz, 1 H), 8.17 (br s, 1 H), 7.80-7.74 (m, 2 H), 7.55 (s, 1 H), 7.52-7.46 (m, 2 H), 7.42 (s, 1 H), 7.24-7.20 (m, 2 H), 7.05 (t, J = 8.6 Hz, 2 H), 6.38 (br d, J = 5.4 Hz, 1 H), 4.27 (t, J = 6.4 Hz, 2 H), 4.03 (s, 3 H), 3.04 (br t, J = 7.2 Hz, 2 H), 2.68 (q, J = 6.8 Hz, 4 H), 1.80-1.68 (m, 2 H), 1.26 (d, J = 6.4 Hz, 6 H), 1.09 (br t, J = 7.2 Hz, 6 H).
52	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl]cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.82 (s, 1H), 8.80 (d, 1H), 8.50 (t, 1H), 7.83 (d, 2H), 7.74 (s, 1H), 7.56 (s, 1H), 7.30-7.38 (m, 4H), 7.15 (t, 2H), 6.80 (d, 1H), 4.32 (d, 2H), 4.04 (s, 3H), 4.03 (s, 3H), 1.42 (s, 4H).
53	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-morpholin-4-ylethyl)cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.62 (s, 1H), 8.79 (d, 1H), 8.24 (t, 1H), 7.83 (d, 2H), 7.72 (s, 1H), 7.58 (s, 1H), 7.37 (d, 2H), 6.76 (d, 1H), 4.04 (s, 3H), 4.03 (s, 3H), 3.98 (m, 2H), 3.66 (m, 2H), 3.49 (m, 4H), 3.25 (t, 2H), 3.13 (br., 2H), 1.42 (d, 4H).

Table 3

Entry	Name	^{1}H-NMR
54	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.78 (s, 1H), 10.53 (s, 1H), 8.43 (d, 1H), 8.12 (d, 1H), 7.82 (d, 2H), 7.49 (s, 1H), 7.37 (s, 1H), 7.20-7.28 (m, 3H), 7.15 (dd, 1H), 7.01 (td, 1H), 6.35 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.47 (s, 2H), 2.17 (br., 4H), 1.49 (m, 4H), 1.41 (m, 4H), 1.32 (br., 2H).
55	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.98 (s, 1H), 10.56 (s, 1H), 8.42 (d, 1H), 8.10 (dd, 1H), 7.81 (m, 2H), 7.49 (s, 1H), 7.37 (s, 1H), 7.17-7.27 (m, 4H), 7.01 (td, 1H), 6.35 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.61 (s, 2H), 2.30 (br., 4H), 1.47 (br., 4H), 1.43 (m, 4H).
56	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.12 (s, 1H), 10.03 (s, 1H), 8.44 (d, 1H), 7.74 (d, 2H), 7.57 (s, 1H), 7.53 (d, 1H), 7.48 (s, 1H), 7.37 (s, 1H), 7.21 (m, 3H), 6.98 (d, 1H), 6.40 (d, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.56 (t, 4H), 3.41 (s, 2H), 2.34 (br., 4H), 1.48 (s, 4H).
57	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.54 (s, 1H), 10.47 (s, 1H), 8.43 (d, 1H), 8.08 (d, 1H), 7.78 (d, 2H), 7.49 (s, 1H), 7.37 (d, 1H), 7.18-7.30 (m, 4H), 7.03 (t, 1H), 6.37 (d, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.50 (s, 2H), 3.44 (br., 4H), 2.20 (br., 4H), 1.48 (d, 4H).
58	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-phenylcyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.14 (s, 1H), 10.03 (s, 1H), 8.44 (d, 1H), 7.74 (d, 2H), 7.62 (d, 2H), 7.48 (s, 1H), 7.37 (s, 1H), 7.27-7.31 (m, 2H), 7.19-7.23 (m, 2H), 7.05 (t, 1H), 6.41 (d, 1H), 3.93 (s, 6H), 3.92 (s, 3H), 1.48 (s, 4H).
59	N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide	1H NMR (400MHz, DMSO-d6): d 10.28 (s, 1H), 10.19 (s, 1H), 8.77 (m, 1H), 8.21 (m, 3H), 7.84 (m, 2H), 7.76 (m, 1H), 7.71 (m, 1H), 7.58 (m, 2H), 7.38 (m, 3H), 7.19 (m, 1H), 6.76 (m, 1H), 4.03 (s, 6H), 3.39 (m, 2H), 1.53 (m, 4H). Note: all peaks are very broad and unresolved.
60	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.0-10.2 (br., 2H), 8.46 (d, 1H), 7.76 (d, 2H), 7.53 (m, 3H), 7.39 (s, 1H), 7.24 (m, 3H), 6.98 (d, 1H), 6.43 (d, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.37 (s, 2H), 2.31 (br., 4H), 1.48 (m, 8H), 1.39 (br., 2H).

Table 3

Entry	Name	^{1}H-NMR
61	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	1H NMR (DMSO-d6): 10.0-10.2 (br., 2H), 8.46 (d, 1H), 7.77 (d, 2H), 7.59 (s, 1H), 7.53 (d, 1H), 7.51 (s, 1H), 7.39 (s, 1H), 7.23 (m, 3H), 6.99 (d, 1H), 6.43 (d, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.52 (s, 2H), 2.42 (br., 4H), 1.69 (br, 4H), 1.48 (s, 4H).

Assays

[0455] Kinase assays were performed by measurement of incorporation of γ-^{33}P ATP into immobilized myelin basic protein (MBP). High binding white 384 well plates (Greiner) were coated with MBP (Sigma #M-1891) by incubation of 60ul/well of 20μg/ml MBP in Tris-buffered saline (TBS; 50mM Tris pH 8.0, 138mM NaCl, 2.7mM KCl) for 24 hours at 4° C. Plates were washed 3X with 100μl TBS. Kinase reactions were carried out in a total volume of 34μl in kinase buffer (5mM Hepes pH 7.6, 15mM NaCl, 0.01% bovine gamma globulin (Sigma #I-5506), 10mM $MgCl_2$, 1mM DTT, 0.02% TritonX-100). Compound dilutions were performed in DMSO and added to assay wells to a final DMSO concentration of 1%. Each data point was measured in duplicate, and at least two duplicate assays were performed for each individual compound determination. Enzyme was added to final concentrations of 10nM or 20nM, for example. A mixture of unlabeled ATP and γ-^{33}P ATP was added to start the reaction ($2x10^6$ cpm of γ-^{33}P ATP per well (3000Ci/mmole) and either 10μM or 30μM unlabeled ATP, typically. The reactions were carried out for 1 hour at room temperature with shaking. Plates were washed 7x with TBS, followed by the addition of 50μl/well scintillation fluid (Wallac). Plates were read using a Wallac Trilux counter. This is only one format of such assays, various other formats are possible, as known to one skilled in the art.

[0456] The above assay procedure can be used to determine the IC_{50} for inhibition and/or the inhibition constant, K_i. The IC_{50} is defined as the concentration of compound required to reduce the enzyme activity by 50% under the conditions of the assay. Exemplary compositions have IC_{50}'s of, for example, less than about 100 μM, less than about 10 μM, less than about 1 μM, and further for example having IC_{50}'s of less than about 100 nM, and still further, for example, less than about 10 nM. The K_i for a compound may be

determined from the IC_{50} based on three assumptions. First, only one compound molecule binds to the enzyme and there is no cooperativity. Second, the concentrations of active enzyme and the compound tested are known (i.e., there are no significant amounts of impurities or inactive forms in the preparations). Third, the enzymatic rate of the enzyme-inhibitor complex is zero. The rate (i.e., compound concentration) data are fitted to the equation:

$$V = V_{max} E_0 \left[I - \frac{(E_0 + I_0 + K_d) - \sqrt{(E_0 + I_0 + K_d)^2 - 4E_0 I_0}}{2E_0} \right]$$

where V is the observed rate, V_{max}, is the rate of the free enzyme, I_0 is the inhibitor concentration, E_0 is the enzyme concentration, and K_d is the dissociation constant of the enzyme-inhibitor complex.

Kinase specificity assays:

[0457] Kinase activity and compound inhibition are investigated using one or more of the three assay formats described below. The ATP concentrations for each assay are selected to be close to the Michaelis-Menten constant (K_M) for each individual kinase. Dose-response experiments are performed at 10 different inhibitor concentrations in a 384-well plate format. The data are fitted to the following four-parameter equation:

$$Y = Min + (Max - Min) / (1 + (X/IC_{50})^{\wedge}H)$$

where Y is the observed signal, X is the inhibitor concentration, Min is the background signal in the absence of enzyme (0% enzyme activity), Max is the signal in the absence of inhibitor (100% enzyme activity), IC_{50} is the inhibitor concentration at 50% enzyme inhibition and H represents the empirical Hill's slope to measure the cooperativity. Typically H is close to unity.

c-Met Assay

[0458] c-Met biochemical activity was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format as described above. Again, kinase activity was measured as the percent ATP remaining following the kinase reaction.

Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 1μM ATP, 1μM poly-EY and 10nM c-Met (baculovirus expressed human c-Met kinase domain P948-S1343) in a 20uL assay buffer (20mM Tris-HCL pH7.5, 10mM $MgCl_2$, 0.02% Triton X-100, 100mM DTT, 2mM $MnCl_2$). The mixture is incubated at ambient temperature for 2hours after which 20uL luciferase-luciferin mix is added and the chemiluminescent signal read using a Wallac Victor^2 reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5ug/mL oxalic acid (pH 7.8), 5 (or 50) mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 uM AMP, 28 ug/mL luciferin and 40,000 units of light/mL luciferase.

KDR Assay

[0459] KDR biochemical activity was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 3 μM ATP, 1.6 μM poly-EY and 5 nM KDR (baculovirus expressed human KDR kinase domain D807-V1356) in a 20uL assay buffer (20mM Tris-HCL pH7.5, 10mM $MgCl_2$, 0.01% Triton X-100, 1mM DTT, 3mM $MnCl_2$). The mixture is incubated at ambient temperature for 4 hours after which 20uL luciferase-luciferin mix is added and the chemiluminescent signal read using a Wallac Victor^2 reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5ug/mL oxalic acid (pH 7.8), 5 (or 50) mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 uM AMP, 28 ug/mL luciferin and 40,000 units of light/mL luciferase.

flt-4 Assay

[0460] Biochemical activity for flt-4 was assessed using an Alphascreen Tyrosine Kinase protocol. AlphaScreen™ (Perkin Elmer) technology is a proximity assay employing microparticles. Singlet oxygen derived from a donor bead following laser excitation results in chemiluminescence when in proximity (100 Å) to an acceptor bead due to biomolecular interactions. For the Flt-4 assay, donor beads coated with streptavidin and acceptor beads coated with PY100 anti-phosphotyrosine antibody were used (Perkin Elmer). Biotinylated poly(Glu,Tyr) 4:1 (Perkin Elmer) was used as the substrate.

Substrate phosphorylation was measured by addition of donor/acceptor beads by chemiluminescence following donor-acceptor bead complex formation. Test compounds, 5 μM ATP, 3 nM biotinylated poly(Glu, Tyr) and 1 nM Flt-4 (baculovirus expressed human Flt-4 kinase domain D725-R1298) were combined in a volume of 20 μL in a 384-well white, medium binding microtiter plate (Greiner). Reaction mixtures were incubated for 1 hr at ambient temperature. Reactions were quenched by addition of 10 uL of 15-30 mg/mL AlphaScreen bead suspension containing 75 mM Hepes, pH 7.4, 300 mM NaCl, 120 mM EDTA, 0.3% BSA and 0.03% Tween-20. After 2-16 hr incubation at ambient temperature plates were read using an AlphaQuest reader (Perkin Elmer). IC_{50} values correlate well with those determined by radiometric assays.

flt-3 Assay

[0461] Biochemical activity for flt-3 was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 5 μM ATP, 3 μM poly-EY and 5 nM Flt-3 (baculovirus expressed human Flt-3 kinase domain R571-S993) in a 20uL assay buffer (20mM Tris-HCL pH7.5, 10mM $MgCl_2$, 0.01% Triton X-100, 1mM DTT, 2mM $MnCl_2$). The mixture is incubated at ambient temperature for 3 hours after which 20uL luciferase-luciferin mix is added and the chemiluminescent signal read using a Wallac Victor^2 reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5ug/mL oxalic acid (pH 7.8), 5 (or 50) mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 uM AMP, 28 ug/mL luciferin and 40,000 units of light/mL luciferase.

c-Kit Assay

[0462] c-Kit biochemical activity was assessed using AlphaScreen ™ (Perkin Elmer) technology, described above. Test compounds, ATP, biotinylated poly(Glu, Tyr) and c-Kit kinase were combined in a volume of 20 μL in a 384-well white, medium binding microtiter plate (Greiner). Reaction mixtures were incubated for 1 hr at ambient temperature. Reactions were quenched by addition of 10 uL of 15-30 mg/mL AlphaScreen bead suspension containing 75 mM Hepes, pH 7.4, 300 mM NaCl, 120 mM

EDTA, 0.3% BSA and 0.03% Tween-20. After 16 hr incubation at ambient temperature plates were read using an AlphaQuest reader (Perkin Elmer).

Structure Activity Relationships

[0463] Table 4 shows structure activity relationship data for selected compounds of the invention. Inhibition is indicated as IC_{50} with the following key: A = IC_{50} less than 50 nM, B = IC_{50} greater than 50 nM, but less than 500 nM, C = IC_{50} greater than 500 nM, but less than 5000 nM, and D = IC_{50} greater than 5,000 nM. Depending upon the functionality about the quinazoline or quinoline, exemplary compounds of the invention exhibit selectivity for any of c-Met, KDR, c-Kit, flt-3, and flt-4. Abbreviations for enzymes listed in Tables 2-3 are defined as follows: c-Met refers to hepatocyte growth factor receptor kinase; KDR refers to kinase insert domain receptor tyrosine kinase; flt-4, fms-like tyrosine kinase-4, representative of the FLK family of receptor tyrosine kinases; c-Kit, also called stem cell factor receptor or steel factor receptor; and flt-3, fms-like tyrosine kinase-3. Empty cells in the tables indicate lack of data only.

Table 4

Entry	Name	c-Met	KDR	c-Kit	flt3	flt4
1	N-[({3-fluoro-4-[(6-(methyloxy)-7-{[(3aR,6aS)-octahydrocyclopenta[c]pyrrol-5-ylmethyl]oxy}quinazolin-4-yl)oxy]phenyl}amino)carbonothioyl]-2-phenylacetamide		A			A
2	N-{[(3-fluoro-4-{[7-({[(3aR,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide	A	A	A		A
3	N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)(methyl)amino]carbonothioyl}-2-phenylacetamide	C				
4	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)imidazolidin-2-one	C		C	C	
5	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)imidazolidin-2-one	C		B	C	
6	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylacetyl)imidazolidin-2-one	B				

7	ethyl [(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](oxo)acetate	B	B	C		B
8	N-{[(4-{[6,7-bis(methyloxy)quinazolin-4-yl]amino}-3-fluorophenyl)amino]carbonothioyl}-2-phenylacetamide	A	B	C		B
9	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)sulfamide	C				
10	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)-1,2,4-oxadiazol-5-amine	C		B	C	
11	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)piperidin-2-one	C		C	C	
12	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(phenylmethyl)ethanediamide	B	B	B	C	B
13	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-phenyl-1,3-thiazol-2-amine	C		C	B	
14	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylethyl)ethanediamide	A	A	A	C	A
15	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-1-phenylmethanesulfonamide	C		C	B	
16	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-2-phenylethanesulfonamide	C		C	C	
17	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(phenylmethyl)benzenesulfonamide	C		C	C	
18	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(phenylmethyl)benzenesulfonamide	C		C	C	
19	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(2-phenylethyl)benzenesulfonamide	C		C	C	
20	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(2-phenylethyl)benzenesulfonamide	C		C	C	
21	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(3-phenylpropyl)benzenesulfonamide	C				
22	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)pyrrolidin-2-one	C		C	B	
23	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (phenylmethyl)carbamate	C				
24	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (2-phenylethyl)carbamate	C				
25	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(3-phenylpropyl)benzenesulfonamide	C				
26	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-phenylethanediamide	B	D	C		C
27	4-{[6,7-bis(methyloxy)quinolin-4-yl]amino}-N-(3-phenylpropyl)benzamide	C				

28	N-{[(3-fluoro-4-{[7-{[(2-methyloctahydrocyclopenta[c]pyrrol-5-yl)methyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide	A	A	A	A	A
29	N-[(Z)-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](imino)methyl]-2-phenylacetamide	C				
30	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-[2-(phenyloxy)ethyl]benzenesulfonamide	C				
31	This type of multiplicative nomenclature is not supported in current version!	C				
32	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-phenylpropane-1-sulfonamide	C				
33	N~2~-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)sulfonyl]-N-phenylglycinamide	C				
34	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-2-phenylacetamide	C				
35	N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide	A	C	D		C
36	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-amine	C		C	C	
37	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-amine	C		C	C	
38	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-phenylacetamide	B	C	D		B
39	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-morpholin-4-ylethyl)ethanediamide	C		B	B	
40	1,1-dimethylethyl {2-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino]-2-oxoethyl}(phenylmethyl)carbamate	C				
41	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-(phenylmethyl)glycinamide	B				
42	N~2~-acetyl-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-(phenylmethyl)glycinamide	C				
43	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-yl)-2-phenylacetamide	B				
44	1,1-dimethylethyl {2-[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)amino]-2-oxoethyl}(phenylmethyl)carbamate	C				
45	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N~2~-(phenylmethyl)glycinamide	C				

46	N~2~-acetyl-N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N~2~-(phenylmethyl)glycinamide	C				
47	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-3-phenylpropanamide	C				
48	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-4-phenylbutanamide	C				
49	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N~2~-methyl-N~2~-(phenylmethyl)glycinamide	C				
50	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[4-(methyloxy)phenyl]ethyl}ethanediamide	C		C	C	
51	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-methyl-N~2~-(phenylmethyl)glycinamide	B	A	B	B	A
52	N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]amino}phenyl)amino]carbonothioyl}-2-phenylacetamide	A	B	B	C	A
53	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-3-phenylpropanamide	C				
54	N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide	A	B	C		B
55	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-1-yl)ethanediamide	A	B	B		B
56	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-2-yl)ethanediamide	C				
57	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-1-yl)ethanediamide	B	B	C		C
58	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-(2-phenylethyl)-N-(phenylmethyl)sulfamide	1470.06				
59	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-(trifluoroacetyl)glycinamide	B	C	B		B
60	N-{2-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino]-2-oxoethyl}benzamide	B	A	A	A	A
61	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N'-(4-fluorophenyl)propanediamide	A	B	B		B
62	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2S)-1,2,3,4-tetrahydronaphthalen-2-yl]ethanediamide	C				

63	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-methylphenyl)ethyl]ethanediamide	C		C	C	
64	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylpropyl)ethanediamide	B	A	B	B	B
65	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-chlorophenyl)ethyl]ethanediamide	A	C	B	C	C
66	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(phenylmethyl)sulfamide	C				
67	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(2-phenylethyl)sulfamide	C				
68	ethyl [(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino](oxo)acetate	C				
69	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)ethanediamide	C				
70	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)propanediamide	A	B	B		C
71	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2R)-1,2,3,4-tetrahydronaphthalen-2-yl]ethanediamide	B	D	B		C
72	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(1-methylpyrrolidin-2-yl)ethyl]ethanediamide	C		C	C	
73	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(phenyloxy)ethyl]ethanediamide	B	B	B		C
74	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-hydroxy-1-(phenylmethyl)ethyl]urea	B				
75	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one	B	B	B	B	B
76	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)ethanediamide	A	B	B	B	B
77	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{[3-(trifluoromethyl)phenyl]methyl}ethanediamide	B		B	B	
78	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[3-(trifluoromethyl)phenyl]ethyl}ethanediamide	C		A	B	
79	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-3-oxo-4-phenylbutanamide	C				

80	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	C				
81	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-[2-(phenyloxy)ethyl]-1,3-benzothiazol-2-amine	B				
82	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-piperidin-1-ylethyl)-1,3-benzothiazol-2-amine	C				
83	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-methyl-N-(2-phenylethyl)-1,3-benzothiazol-2-amine	C				
84	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-pyrrolidin-1-ylethyl)-1,3-benzothiazol-2-amine	C				
85	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{[3-(trifluoromethyl)phenyl]methyl}-1,3-benzothiazol-2-amine	C				
86	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{2-[3-(trifluoromethyl)phenyl]ethyl}-1,3-benzothiazol-2-amine	C				
87	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-[3-(trifluoromethyl)phenyl]propanediamide	C				
88	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	C	A	B	B	B
89	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-{[3-(trifluoromethyl)phenyl]methyl}glycinamide	B	A	B	B	A
90	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-(2-phenylethyl)glycinamide	B				
91	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide	B	B	B	B	A
92	1,1-dimethylethyl {2-[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino]-2-oxoethyl}(phenylmethyl)carbamate	C				
93	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N~2~-(phenylmethyl)glycinamide	C				
94	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3,5-bis(trifluoromethyl)phenyl]acetamide	C	B	B	D	C
95	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[2-chloro-5-(trifluoromethyl)phenyl]acetamide	A	A	B	B	B
96	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(2-phenylethyl)ethanediamide	A	A	A	A	A

97	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)ethanediamide	C				
98	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]ethanediamide	B	B	B	A	B
99	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-methyl-N~2~-{[3-(trifluoromethyl)phenyl]methyl}glycinamide	C				
100	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-methyl-N~2~-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide	C				
101	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N~2~-methyl-N~2~-(2-phenylethyl)glycinamide	C				
102	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-(phenylmethyl)imidazolidin-2-one	B	B	B	B	C
103	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridazin-3-yl)-N'-(4-fluorophenyl)propanediamide	A	C	B	A	C
104	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-chlorophenyl)propanediamide	B				
105	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(3-chlorophenyl)propanediamide	C				
106	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N~2~-methyl-N~2~-(phenylmethyl)glycinamide	C				
107	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-chlorophenyl)propanediamide	B				
108	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(methyloxy)imino]propanamide	B	B			
109	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(ethyloxy)imino]propanamide	B	A			
110	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-{[(phenylmethyl)oxy]imino}propanamide	B	B			
111	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-1-(phenylmethyl)prolinamide	C	C			
112	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one	B	C	B	C	C
113	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)imidazolidin-2-one	C	C			

114	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)-4,5-dihydro-1,3-oxazol-2-amine	C	B			
115	6,7-bis(methyloxy)-4-({4-[4-(phenylmethyl)piperazin-1-yl]phenyl}oxy)quinoline	C	C			
116	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)piperazin-2-one	C	C			
117	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N~2~-(phenylmethyl)alaninamide	C	C			
118	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N~2~-methyl-N~2~-(phenylmethyl)alaninamide	C	C			
119	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N~2~-(phenylmethyl)leucinamide	C	C			
120	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N~2~-methyl-N~2~-(phenylmethyl)leucinamide	C	C			
121	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N~2~-(phenylmethyl)valinamide	C	C			
122	N-[5-chloro-6-({6-(methyloxy)-4-[(piperidin-4-ylmethyl)oxy]quinolin-7-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)propanediamide	C	C			
123	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)tetrahydropyrimidin-2(1H)-one	C	C			
124	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-phenylethyl)ethanediamide	A	A	A	A	A
125	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	A	B
126	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	C	C			
127	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N~2~-methyl-N~2~-(phenylmethyl)valinamide	C	C			
128	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(phenyloxy)imino]propanamide	C	A			
129	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-phenyl-2-{[(phenylmethyl)oxy]imino}ethanamide	B	C			
130	6,7-bis(methyloxy)-4-({4-[4-(phenylmethyl)piperidin-1-yl]phenyl}oxy)quinoline	C	C			
131	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{[2-(1-methylethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]methyl}ethanediamide	B	B			
132	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2-ethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]ethanediamide	B	C			

133	1,1-dimethylethyl 4-({[4-{[3-chloro-5-({3-[(4-fluorophenyl)amino]-3-oxopropanoyl}amino)pyridin-2-yl]oxy}-6-(methyloxy)quinolin-7-yl]oxy}methyl)piperidine-1-carboxylate	B	C			
134	N-[5-chloro-6-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)propanediamide	A	B	B	A	
135	N-{5-chloro-6-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]pyridin-3-yl}-N'-(4-fluorophenyl)propanediamide	A	B	B	A	
136	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylethyl)ethanediamide	A	A	A	B	A
137	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-phenylethyl)ethanediamide	A	A	A	B	A
138	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-phenylethyl)ethanediamide	A	A	A	A	
139	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylethyl)ethanediamide	A	A	A	A	A
140	N'-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N-methyl-N-(2-phenylethyl)ethanediamide	A	A			B
141	N-(3-fluoro-4-{[7-({[(3aR,5r,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-phenylethyl)ethanediamide	A	A	A	A	A
142	N-(3-fluoro-4-{[7-({[(3aR,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-yl]oxy}phenyl)-N'-(2-phenylethyl)ethanediamide	A	A	A	A	A
143	2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-2-oxoacetamide	A	A			
144	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-2-oxo-2-(3-phenylpyrrolidin-1-yl)acetamide	A	A	A	A	A
145	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-2-oxo-2-(2-phenylmorpholin-4-yl)acetamide	A	B	B	B	

146	N-[2-(dimethylamino)-2-phenylethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	B	A	
147	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-oxo-2-phenylethyl)ethanediamide	A	B	B	B	B
148	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-2,2-difluoro-N'-(4-fluorophenyl)propanediamide	C	C			
149	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(phenylmethyl)ethanediamide	A	A	A	B	A
150	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(2-fluorophenyl)ethyl]ethanediamide	A	A	A	A	A
151	N-[2-(3-chlorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
152	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[2-(methyloxy)phenyl]ethyl}ethanediamide	A	A	A	A	A
153	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-pyridin-3-ylethyl)ethanediamide	A	B	B	B	
154	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(phenylmethyl)ethanediamide	A	A	A	B	A
155	N-{2-[2,5-bis(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
156	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[2-(trifluoromethyl)phenyl]ethyl}ethanediamide	A	A	A	A	C
157	N-{2-[2-(ethyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
158	N-[2-(2,4-dimethylphenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	A	B
159	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1S)-2-(4-methylphenyl)-1-phenylethyl]ethanediamide	B	C			
160	N-[2-(4-chlorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	B

161	({3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}amino)(oxo)acetic acid	B	C			
162	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(3-fluorophenyl)ethyl]ethanediamide	A	A			A
163	N-[2-(2-chlorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	B	A
164	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[3-(methyloxy)phenyl]ethyl}ethanediamide	A	A	A	A	A
165	N-(1,2-diphenylethyl)-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	B	B	C
166	N-[2-(2,4-dichlorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	A	B
167	N-{2-[3,4-bis(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	
168	N-[2-(4-ethylphenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	C
169	N-{2-[4-(ethyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	B	C	B	B	
170	N-{2-[4-(ethyloxy)-3-(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	C	B	
171	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[4-(phenyloxy)phenyl]ethyl}ethanediamide	B	C	C	C	
172	N-{2-[3-(ethyloxy)-4-(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	C	B	B	
173	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-pyridin-2-ylethyl)ethanediamide	A	A	A	B	B
174	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-pyridin-4-ylethyl)ethanediamide	A	B	B	B	C
175	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(4-fluorophenyl)ethyl]ethanediamide	A	A	A	A	A

176	N-[2-(2-bromophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
177	N-[2-(2-chloro-6-fluorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	B	A
178	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(2R)-2-phenylpropyl]ethanediamide	A	A	A	B	A
179	N-(2,3-dihydro-1H-inden-1-yl)-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
180	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(2-methylpropyl)ethanediamide	A	B	B	B	
181	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(3-methylbutyl)ethanediamide	A	B	B	B	B
182	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-[(2R)-2-phenylpropyl]ethanediamide	A	A	A	A	A
183	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(2-phenylpropyl)ethanediamide	A	A	A	A	A
184	N-(2,3-dihydro-1H-inden-2-yl)-N'-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}ethanediamide	A	A	A	B	A
185	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1R)-1-phenylethyl]ethanediamide	A	B	B	B	
186	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1S)-1-phenylethyl]ethanediamide	A	B	A	B	C
187	N-[2-(3-bromophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
188	N-[2-(2,6-dichlorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
189	N-[2-(1,3-benzodioxol-5-yl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	B	A	B

190	N-{5-chloro-6-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]pyridin-3-yl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	A	A
191	N-{2-[3-bromo-4-(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	B	B	B
192	N-{2-[3,5-bis(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	B	B
193	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(2-methylphenyl)ethyl]ethanediamide	A	A	A	B	A
194	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(3-methylphenyl)ethyl]ethanediamide	A	A	A	A	A
195	N-{2-[3-(ethyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	B	B	B
196	N-[2-(3,4-dimethylphenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	B	B	B
197	N-[2-(2,5-dimethylphenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
198	N-{2-[3-chloro-4-(propyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	B	C			
199	N-{2-[4-(butyloxy)-3-chlorophenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	B	C			
200	N-{2-[4-(1,1-dimethylethyl)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	B	C			
201	N-{2-[4-(aminosulfonyl)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	B
202	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[4-hydroxy-3-(methyloxy)phenyl]ethyl}ethanediamide	A	B	B	A	B
203	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[3-hydroxy-4-(methyloxy)phenyl]ethyl}ethanediamide	A	B	B	B	B
204	N-[(2,4-dichlorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	B

205	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}ethanediamide	A	A	B	A	A
206	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1R)-1-(4-methylphenyl)ethyl]ethanediamide	A	B	B	B	B
207	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[3-fluoro-4-(trifluoromethyl)phenyl]methyl}ethanediamide	A	B	B	B	B
208	N-[(3-chloro-4-fluorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	B
209	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{(1S)-1-[3-(methyloxy)phenyl]ethyl}ethanediamide	A	B	B	B	B
210	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1R)-1-naphthalen-2-ylethyl]ethanediamide	A	B	B	B	
211	N-{[4-chloro-3-(trifluoromethyl)phenyl]methyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
212	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1S)-1-(4-methylphenyl)ethyl]ethanediamide	A	B	C	B	
213	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[6-(trifluoromethyl)pyridin-3-yl]methyl}ethanediamide	A	B	C	B	B
214	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(2-methylphenyl)methyl]ethanediamide	A	A	A	A	B
215	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(3-methylphenyl)methyl]ethanediamide	A	A	A	B	A
216	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}ethanediamide	A	A	B	A	A
217	N-[(3,5-dichlorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
218	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1R)-1,2,3,4-tetrahydronaphthalen-1-yl]ethanediamide	A	B	B	B	A

219	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1S)-1,2,3,4-tetrahydronaphthalen-1-yl]ethanediamide	A	A	A	A	A
220	N-cyclopentyl-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	B
221	N-[1-(4-bromophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	B
222	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(2-fluorophenyl)methyl]ethanediamide	A	A	B	B	A
223	N-[2-(3,4-dichlorophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	
224	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(4-fluorophenyl)methyl]ethanediamide	A	A	A	A	A
225	N-[(2,3-difluorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	B	B	A
226	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(phenyloxy)ethyl]ethanediamide	A	A	A	A	A
227	N-(2,2-diphenylethyl)-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	A	B
228	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{2-[4-(methyloxy)phenyl]ethyl}ethanediamide	A	B	B	B	B
229	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-phenylpropyl)ethanediamide	A	A	A	A	A
230	N-[2-(4-bromophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	B	B	B
231	N-(4-{[7-{[(1-ethylpiperidin-4-yl)methyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-2-oxo-2-(2-phenylmorpholin-4-yl)acetamide	A	B	B	B	B
232	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[3-fluoro-5-(trifluoromethyl)phenyl]methyl}ethanediamide	A	A	B	A	B
233	N-[(3,5-difluorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	B	A

234	N-{[2-chloro-5-(trifluoromethyl)phenyl]methyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	B	A	B
235	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(dimethylamino)-2-phenylethyl]ethanediamide	B	B	B	A	
236	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[4-(methyloxy)phenyl]methyl}ethanediamide	A	A	A	B	B
237	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[4-(trifluoromethyl)phenyl]methyl}ethanediamide	A	B	B	B	A
238	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[3-(methyloxy)phenyl]methyl}ethanediamide	A	A	A	A	B
239	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[3-(trifluoromethyl)phenyl]methyl}ethanediamide	A	A	A	A	B
240	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-({3-[(trifluoromethyl)oxy]phenyl}methyl)ethanediamide	A	A	A	A	A
241	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[2-(methyloxy)phenyl]methyl}ethanediamide	A	A	A	A	A
242	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[2-(trifluoromethyl)phenyl]methyl}ethanediamide	A	A	A	A	A
243	N-[(3-chlorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	B	B
244	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-({2-[(trifluoromethyl)oxy]phenyl}methyl)ethanediamide	A	A	A	A	A
245	N-[(2-chlorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
246	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-({4-[(trifluoromethyl)oxy]phenyl}methyl)ethanediamide	A	B	B	B	B
247	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-{[4-(methyloxy)phenyl]methyl}ethanediamide	A	B	A	B	
248	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-{[4-(trifluoromethyl)phenyl]methyl}ethanediamide	A	B	B	B	B

249	N-(4-{[7-[(azetidin-3-ylmethyl)oxy]-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylethyl)ethanediamide	A	A			
250	N-(3-fluoro-4-{[7-{[(1-methylazetidin-3-yl)methyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-phenylethyl)ethanediamide	A	A	A	A	A
251	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-hydroxy-2-phenylethyl)ethanediamide	B	B	B	B	
252	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2,4-difluorophenyl)propanediamide	A	C			
253	N'-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N-(4-fluorophenyl)-N-methylpropanediamide	B	C			
254	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1R)-1-phenylpropyl]ethanediamide	A	B	B	B	B
255	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1S)-1-phenylpropyl]ethanediamide	A	B	C	B	
256	N-[(3,4-difluorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	B	A
257	N-[(2,6-difluorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	B	A
258	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-[2-(4-fluorophenyl)ethyl]ethanediamide	A	A	A	A	A
259	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-phenylethanediamide	A	B	C	C	B
260	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(3-fluorophenyl)ethanediamide	A	C	B	C	C
261	N-(3-chloro-4-fluorophenyl)-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	C	C	B	B
262	N-[3,4-bis(methyloxy)phenyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	C	C	B	B
263	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(3-methylbutyl)ethanediamide	A	B	A	B	B

264	N-(3,3-dimethylbutyl)-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	B
265	N-[5-chloro-6-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)propanediamide	A	B	B	A	B
266	N-[5-chloro-6-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)propanediamide	A	B	B	A	B
267	N-(5-chloro-6-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N'-(4-fluorophenyl)propanediamide	A	B	B	A	B
268	N-[(4-chlorophenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A			
269	N-{[3,5-bis(methyloxy)phenyl]methyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A		A	
270	N-[(4-butylphenyl)methyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	B
271	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(4-methylphenyl)ethyl]ethanediamide	A	B	B	A	B
272	N-{[3,5-bis(trifluoromethyl)phenyl]methyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	C	B	
273	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(pyrazin-2-ylmethyl)ethanediamide	B	C	C	B	
274	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(pyridin-2-ylmethyl)ethanediamide	A	B	B	B	B
275	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(2-phenylethyl)ethanediamide	A	A	A	A	A
276	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(2-phenylethyl)ethanediamide	A	A	A	A	A
277	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[2-fluoro-3-(trifluoromethyl)phenyl]methyl}ethanediamide	A	A	A	A	A
278	N-{2-[2-bromo-6-(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A

279	N-{2-[3,4-bis(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N-methylethanediamide	B	B	B	A	B
280	N-{2-[5-bromo-2-(methyloxy)phenyl]ethyl}-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	A	A	A	A
281	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-{[2-fluoro-5-(trifluoromethyl)phenyl]methyl}ethanediamide	A	A	B	A	B
282	N-[5-chloro-6-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
283	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[1-(4-fluorophenyl)ethyl]ethanediamide	A	A	B	A	B
284	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[(1S)-2-oxo-1-(phenylmethyl)-2-pyrrolidin-1-ylethyl]ethanediamide	A	C	B	B	C
285	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(3aR,6aS)-octahydrocyclopenta[c]pyrrol-5-ylmethyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(2-phenylethyl)ethanediamide	A	A	A	A	A
286	N-[2-(4-aminophenyl)ethyl]-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	B
287	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-2-oxo-2-[4-(phenylmethyl)piperidin-1-yl]acetamide	A	A	B	A	B
288	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)propanediamide	A	A	A	A	A
289	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	5.581
290	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(3-fluorophenyl)propanediamide	B	C			
291	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-phenylpropanediamide	A	C	B	A	C
292	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)-2,2-dimethylpropanediamide	B	B	B	A	B
293	N-ethyl-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	B

294	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(1-methylethyl)ethanediamide	A	B	B	B	C
295	N-butyl-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	B
296	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-[2-(methyloxy)ethyl]ethanediamide	B	B	B	B	C
297	N-(cyclopropylmethyl)-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]ethanediamide	A	B	B	B	B
298	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(2-morpholin-4-ylethyl)ethanediamide	B	A	B	A	B
299	N-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-2-oxo-2-pyrrolidin-1-ylacetamide	A	B	B	B	B
300	N-ethyl-N'-[3-fluoro-4-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)phenyl]-N-methylethanediamide	A	B	C	B	B
301	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(phenylmethyl)cyclopropane-1,1-dicarboxamide	A	C	B	B	B
302	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)cyclopropane-1,1-dicarboxamide	C	C			
303	N-{4-[(7-chloroquinolin-4-yl)oxy]-3-fluorophenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	C	C	B
304	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
305	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-phenylcyclopropane-1,1-dicarboxamide	A	B	B	A	
306	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	B	B	C	B
307	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	A	A	A	B	A
308	N-{4-[(7-chloroquinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	C	B
309	N-[5-chloro-6-({6-(methyloxy)-7-[(phenylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	C	C	B	C

310	N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
311	N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	A	A
312	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
313	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
314	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	A	A	A	B	A
315	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
316	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
317	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	C	A
318	N-(4-fluorophenyl)-N'-[2-methyl-6-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]cyclopropane-1,1-dicarboxamide	A	A	B	B	B
319	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
320	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloro-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	C	C	B	C
321	N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	A	A
322	N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
323	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	A	A
324	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A

325	N-{3-fluoro-4-[(7-(methyloxy)-6-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	A	A
326	N-[5-fluoro-2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	B	B
327	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,3,5-trifluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	B	B
328	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	B	B	C	C
329	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	B	B	C	B
330	N-(3-fluoro-4-{[6-hydroxy-7-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
331	N-(4-fluorophenyl)-N'-[2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide	A	A	A	B	A
332	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
333	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
334	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
335	N-(4-fluorophenyl)-N'-[4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide	A	A	A	A	A
336	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
337	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	B	B	C	C
338	N-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	C	C			

339	N-(4-fluorophenyl)-N'-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide	C	C			
340	N-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	C	C			
341	N-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	C	C			
342	(1S,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A	B	A	A
343	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A	A	A	A
344	N-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A		A	
345	N-(4-{[6-{[2-(diethylamino)ethyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A		A	
346	1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[(1-{[(4-fluorophenyl)amino]carbonyl}cyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate	A	A		B	
347	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A			
348	(1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		B	
349	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A		A	
350	N-(4-{[7-{[3-(4-acetylpiperazin-1-yl)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A		A	
351	1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[((1R,2R)-1-{[(4-fluorophenyl)amino]carbonyl}-2-methylcyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate	A	A		B	

352	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide	A	C		C	
353	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)azetidine-3,3-dicarboxamide	B	C		C	
354	(1R,2S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
355	(1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
356	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
357	N-(3-fluoro-4-{[7-({3-[4-(1-methylethyl)piperazin-1-yl]propyl}oxy)-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A		A	
358	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A		A	
359	(1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
360	(1R,2R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
361	(1R,2S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
362	(1R,2S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
363	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	A	A			
364	(1R,2S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	

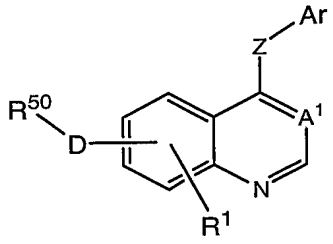
365	(1r,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	B		B	
366	(1r,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	B		B	
367	(1r,2R,3S)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	B	A		B	
368	(1r,2R,3S)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	A		B	
369	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	B	A		B	
370	(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	A		B	
371	(2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	A		B	
372	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	A	A		B	
373	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	A	A		C	
374	(1r,2R,3S)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	B		B	
375	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	A	A		C	
376	(1r,2R,3S)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	B		B	

377	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	A	A		B	
378	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	A	B		C	
379	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide	A	A		C	
380	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	A	A		B	
381	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	A	A		B	
382	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	A	A		B	
383	(2R,3R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	A		C	
384	N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	A	A		C	
385	N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	A	A		C	
386	(1R,2R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
387	(1R,2R)-N-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
388	(2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	B	A		C	

389	(2R,3R)-N-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	A		B	
390	(1R,2R)-N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide	A	A		A	
391	(2R,3R)-N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide	A	A		B	
392	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[(4-fluorophenyl)methyl]cyclopropane-1,1-dicarboxamide	B	B		A	
393	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(2-morpholin-4-ylethyl)cyclopropane-1,1-dicarboxamide	C	D		B	
394	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	B	D		B	
395	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	B	C		B	
396	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	B	A		A	
397	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[2-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	B	C		B	
398	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-phenylcyclopropane-1,1-dicarboxamide	A	A		A	
399	N-[3-(aminomethyl)phenyl]-N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide	B	A		B	
400	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	B	A			
401	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-[3-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide	A	A			

What is claimed is:

1. A compound for modulating kinase activity according to formula **I**,



I

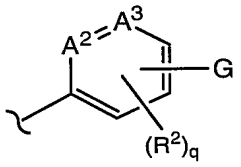
or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

R^1 is selected from -H, halogen, $-OR^3$, $-NO_2$, $-NH_2$, $-NR^3R^4$, and optionally substituted lower alkyl;

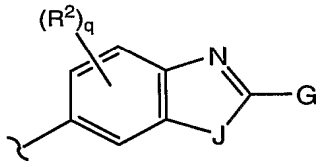
A^1 is selected from =N-, =C(H)-, and =C(CN)-;

Z is selected from $-S(O)_{0-2}$-, -O-, and $-NR^5$-;

Ar is either a group of formula **II**, or of formula **III**,



II



III

wherein,

R^2 is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

q is 0 to 4;

G is a group -B-L-T, wherein

B is selected from absent, $-N(R^{13})$-, $-N(SO_2R^{13})$-, -O-, $-S(O)_{0-2}$-, and -C(=O)-;

L is selected from absent, $-C(=S)N(R^{13})$-, $-C(=NR^{14})N(R^{13})$-, $-SO_2N(R^{13})$-, $-SO_2$-, $-C(=O)N(R^{13})$-, $-N(R^{13})$-, $-C(=O)C_{1-2}$alkyl$N(R^{13})$-, $-N(R^{13})C_{1-2}$alkylC(=O)-, $-C(=O)C_{0-1}$alkylC(=O)$N(R^{13})$-, $-C_{0-4}$alkylene-, $-C(=O)C_{0-1}$alkylC(=O)OR^3-, $-C(=NR^{14})C_{0-1}$alkylC(=O)-, -C(=O)-, $-C(=O)C_{0-1}$alkylC(=O)-, and an optionally substituted four to six-membered heterocyclyl containing

between one and three annular heteroatoms including at least one nitrogen; and

T is selected from -H, -R^{13}, -C_{0-4}alkyl, -C_{0-4}alkylQ, -OC_{0-4}alkylQ, -C_{0-4}alkylOQ, -$N(R^{13})C_{0-4}$alkylQ, -SO_2C_{0-4}alkylQ, -$C(=O)C_{0-4}$alkylQ, -C_{0-4}alkyl$N(R^{13})$Q, and -$C(=O)N(R^{13})C_{0-4}$alkylQ, wherein each of the aforementioned C_{0-4}alkyl is optionally substituted;

J is selected from -$S(O)_{0-2}$-, -O-, and -NR^{15}-;

R^3 is -H or R^4;

R^4 is selected from optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, and optionally substituted lower heterocyclylalkyl; or

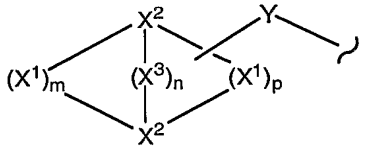
R^3 and R^4, when taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl, said optionally substituted five- to seven-membered heterocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

A^2 and A^3 are each independently selected from =N-, =$C(R^2)$-;

R^5 is -H or optionally substituted lower alkyl;

D is selected from -O-, -$S(O)_{0-2}$-, and -NR^{15}-;

R^{50} is either R^3, or according to formula **IV**;



IV

wherein X^1, X^2, and optionally X^3, represent the atoms of a saturated bridged ring system, said saturated bridged ring system comprising up to four annular heteroatoms represented by any of X^1, X^2, and X^3; wherein,

each X^1 is independently selected from -$C(R^6)R^7$-, -O-, -$S(O)_{0-2}$-, and -NR^8-;

each X^2 is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each X^3 is independently selected from -$C(R^6)R^7$-, -O-, -$S(O)_{0-2}$-, and -NR^8-;

Y is either:

an optionally substituted lower alkylene linker, between D and either 1) any annular atom of the saturated bridged ring system, except X^2 when X^2 is a bridgehead nitrogen, or 2) any heteroatom, represented by any of R^6 or R^7; provided there are at least two carbon atoms between D and any annular heteroatom of the saturated bridged ring system or any heteroatom represented by any of R^6 or R^7;

or Y is absent, when Y is absent, said saturated bridged ring system, is directly attached to D via an annular carbon of said saturated bridged ring system, unless D is $-SO_2-$, in which case said saturated bridged ring system, is directly attached to D via an any annular atom of said saturated bridged ring system;

m and p are each independently 1-4;

n is 0-2, when n = 0, then there is a single bond between the two bridgehead X^2's;

R^6 and R^7 are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^4$, $-SO_2NR^3R^4$, $-CO_2R^3$, $-C(O)NR^3R^4$, $-N(R^3)SO_2R^4$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, optionally substituted lower heterocyclylalkyl, and a bond to either Y or D; or

R^6 and R^7, when taken together are oxo; or

R^6 and R^7, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclyl, said optionally substituted three- to seven-membered spirocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

R^8 is selected from $-R^3$, Y, $-SO_2NR^3R^4$, $-CO_2R^4$, $-C(O)NR^3R^3$, $-SO_2R^4$, and $-C(O)R^3$;

R^{13} is selected from -H, $-C(=O)R^3$, $-C(=O)OR^3$, $-C(=O)SR^3$, $-SO_2R^4$, $-C(=O)N(R^3)R^3$, and optionally substituted lower alkyl,

two R^{13}, together with the atom or atoms to which they are attached, can combine to form a heteroalicyclic optionally substituted with between one and four of R^{60}, said heteroalicyclic can have up to four annular heteroatoms, and said heteroalicyclic can have

an aryl or heteroaryl fused thereto, in which case said aryl or heteroaryl is optionally substituted with an additional one to four of R^{60};

R^{14} is selected from -H, $-NO_2$, $-NH_2$, $-N(R^3)R^4$, -CN, $-OR^3$, optionally substituted lower alkyl, optionally substituted heteroalicyclylalkyl, optionally substituted aryl, optionally substituted arylalkyl and optionally substituted heteroalicyclic;

R^{15} is a group $-M^1-M^2$, wherein M^1 is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-C(=O)C(=O)N(R^{13})-$, $-C_{0-4}$alkylene-, -C(=O)-, and an optionally substituted four to six-membered hetercyclyl annular containing between one and three heteratoms including at least one nitrogen; and M^2 is selected from -H, $-C_{0-6}$alkyl, alkoxy, $-C(=O)C_{0-4}$alkylQ, $-C_{0-4}$alkylQ, $-OC_{0-4}$alkylQ-, $-N(R^{13})C_{0-4}$alkylQ-, and $-C(=O)N(R^{13})C_{0-4}$alkylQ; and

Q is a five- to ten-membered ring system, optionally substituted with between zero and four of R^{20};

R^{20} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted lower alkyl;

R^{60} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroarylalkyl, and optionally substituted arylalkyl;

two of R^{60}, when attached to a non-aromatic carbon, can be oxo;

with the proviso, only when Ar is according to formula **II**, if Y is a C_{1-6} alkylene; Z is -NH- or $-N(CH_3)-$; R^1 is a C_{1-6}alkyl optionally substituted in the 2-position by -OH or a C_{1-4}alkoxy group; R^2 is -H or halogen; n = 0; and the atoms, X^1, of one bridge of the saturated bridged ring system, when combined with both bridgehead atoms, X^2, of the saturated bridged ring system, represent:

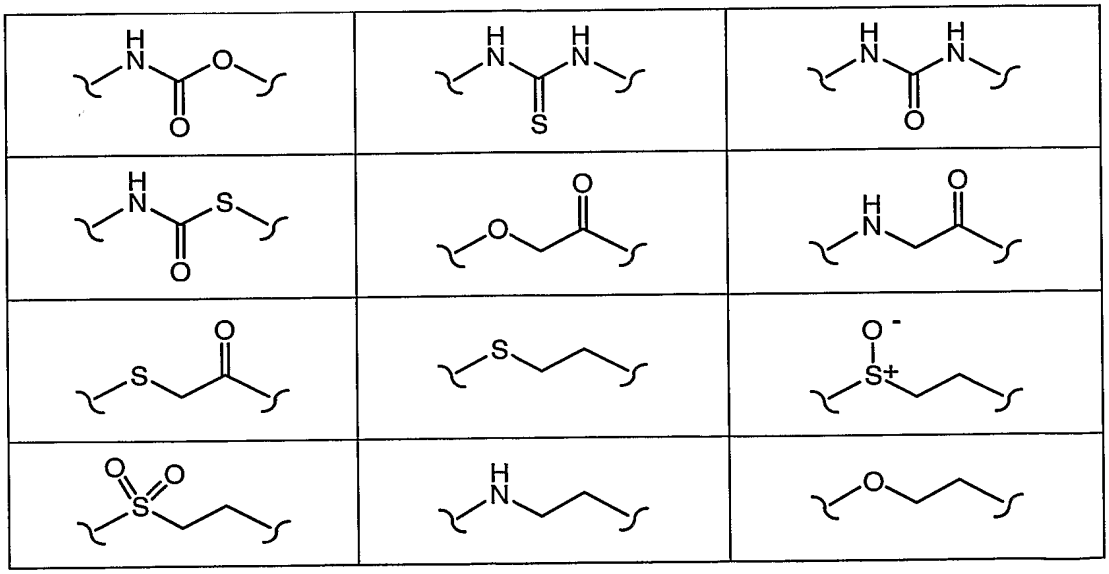
1) either a pyrrolidine or a piperidine, and any atom, X^1 or X^2, of either of said pyrrolidine or said piperidine is attached to Y, then the other bridge of said saturated bridged ring system cannot be any one of $-OC(O)CH_2-$, $-CH_2OC(O)-$, $-OC(O)CH_2CH_2-$, $-CH_2OC(O)CH_2-$, $-CH_2CH_2OC(O)-$, $-OC(O)CH_2NH-$, $-OC(O)CH_2N(C_{1-4}alkyl)-$, and $-OC(O)CH_2O-$; or

2) either a piperazine or a 4-(C_{1-4}alkyl)-piperazine, and any atom, X^1 or X^2, of either of said piperazine or said 4-(C_{1-4}alkyl)-piperazine is attached to Y, then the other bridge of said saturated bridged ring system, only when attached via the 2- and the 3-position of either of said piperazine or said 4-(C_{1-4}alkyl)-piperazine, cannot be one of $-CH_2OC(O)CH_2-$, $-CH_2CH_2OC(O)-$, and either of the two aforementioned bridges optionally substituted by one or two C_{1-2}alkyl groups; or

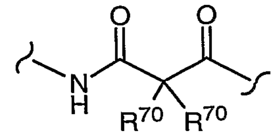
3) a piperazine, and any atom, X^1 or X^2, of said piperazine is attached to Y, then the other bridge of said saturated bridged ring system, only when attached via the 3- and the 4-position of said piperazine, cannot be one of $-C(O)OCH_2CH_2-$, $-CH_2OC(O)CH_2-$, and either of the two aforementioned bridges optionally substituted by one or two C_{1-2}alkyl groups, and only when either of the two aforementioned bridges are attached to the 3-position of said piperazine via their left-hand end as depicted above; or

4) a 2-oxomorpholine, said 2-oxomorpholine attached to Y via its 4-position, then the other bridge of said saturated bridged ring system, only when attached via the 5- and the 6-position of said 2-oxomorpholine, cannot be one of $-(CH_2)_g-$, $-CH_2WCH_2-$, $-CH_2WCH_2CH_2-$, and $-CH_2CH_2WCH_2-$, wherein W is -O-, $-S(O)_{0-2}-$, -NH-, or $-N(C_{1-4}$alkyl)- wherein g is 2, 3, or 4;

and with the proviso that when Z is-O-, Ar is according to formula **II**, and the portion of G directly attached to Ar is selected from:



then R^{50} must be of formula **IV**;

and with the proviso that when Ar is phenylene or substituted phenylene, Z is -S(O)$_{0\text{-}2}$- or -O-, then the portion of G directly attached to Ar cannot contain  , when R^{70} is selected from -H, $C_{1\text{-}4}$alkyl, and $C_{1\text{-}4}$alkoxyl.

2. The compound according to claim 1, wherein In one example, the compound is according to paragraph [0033], wherein Z is either -O- or -NR^5-.

3. The compound according to claim 2, wherein G is selected from the following: